Original Article

Impact of the Commercialization of Three Generic Angiotensin II Receptor Blockers on Adverse Events in Quebec, Canada

A Population-Based Time Series Analysis

Jacinthe Leclerc, RN, MSc; Claudia Blais, PhD; Louis Rochette, MSc; Denis Hamel, MSc; Line Guénette, BPharm, PhD; Paul Poirier, MD, PhD

Background—Once the patent of a brand-name drug expires, generic drugs are commercialized, and substitution from brand-name to generics may occur. Generic drug equivalence is evaluated through comparative bioavailability studies. Few studies have assessed outcomes after generic drug commercialization at a population level. We evaluated the impact of 3 generic angiotensin II receptor blockers commercialization on adverse events: hospitalizations or emergency room consultations.

Methods and Results—This is an interrupted time series analysis using the Quebec Integrated Chronic Disease Surveillance System. Rates of adverse events for losartan, valsartan, and candesartan users (N=136 177) aged ≥66 years were calculated monthly, 24 months before and 12 months after generics commercialization. Periods before and after generics commercialization were compared by negative binomial segmented regression models. Sensitivity analyses were also conducted. For all users, there was a monthly mean rate of 100 adverse events for 1000 angiotensin II receptor blocker users before and after generic commercialization. Among generic users of losartan, valsartan, and candesartan, there was an increase in rates of adverse events of 8.0% (difference of proportions versus brand-name, 7.5% [95% confidence interval, −0.9% to 15.9%]; P=0.0643), 11.7% (difference of proportions, 17.1% [95% confidence interval, 9.9%–24.3%]; P<0.0001), and 14.0% (difference of proportions, 16.6% [95% confidence interval, 7.9%–25.3%]; P<0.0001), respectively, the month of generic commercialization. The monthly trend of adverse events was affected for generic versus brand-name losartan users only (difference of proportions, 2.0% [0.7%–3.4%]; P=0.0033) ≤1 year after generics commercialization. Similar results were found in sensitivity analyses.

Conclusions—Among generic users, immediate or delayed differences in adverse events rates were observed right after generic commercialization for 3 antihypertensive drugs. Rates of adverse events remained higher for generic users. Increases were more pronounced for generic candesartan, which is the studied product with the largest difference in comparative bioavailability. Risk and survival analysis studies controlling for several potential confounding factors are required to better characterize generic substitution. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003891. DOI: 10.1161/CIRCOUTCOMES.117.003891.)**

Key Words: adverse events complications ■ angiotensin II receptor blockers ■ brand-name drugs ■ generic drugs ■ pharmacoepidemiology

Generic drugs are alternatives to brand-name drugs once the patent expires. Known as being generally less expensive, they are economically beneficial for patients, healthcare systems, and third-party payers.[1–4] To achieve substantial healthcare cost reductions, the provincial government of Quebec, Canada, promotes generic substitutions and restricts access to brand-name drugs by economical and administrative strategies.[5] Once generic analogs become available, market is then shared between brand-name and generics, but little is published about the rate of this market sharing, neither regarding the clinical impact of generics commercialization.

See Editorial by Alter

Generic and brand-name drugs are assumed to be clinically equivalent and are used interchangeably once approved

Received September 13, 2016; accepted July 31, 2017.

From the Bureau d'Information en Santé des Populations, Institut national de santé publique du Québec (J.L., C.B., L.R., D.H.), Faculté de Pharmacie, Université Laval (J.L., C.B., L.G., P.P.), Department of Nursing, Université du Québec à Trois-Rivières (J.L.), Centre de recherche du CHU de Québec, Axe Santé des populations et pratiques optimales en santé (L.G.), and Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec (P.P.), Canada.

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.117.003891/-/DC1.

Correspondence to Paul Poirier, MD, PhD, Institut universitaire de cardiologie et de pneumologie de Québec, Faculté de Pharmacie, Université Laval, 2725 Chemin Sainte-Foy, Québec, QC, Canada, G1V 4G5. E-mail paul.poirier@criucpq.ulaval.ca

WHAT IS KNOWN

- Generic drugs are licensed by health authorities following acceptable data from comparative bioavailability studies. Of the few studies that have assessed the impact of generic drugs commercialization on outcomes in the population treated in cardiology, most have found discordant results.

WHAT THE STUDY ADDS

- The population using generic angiotensin II receptor blockers had higher rates of hospitalizations and emergency room consultations.
- The difference was most pronounced in the first month and with candesartan.
- These important results merit further attention through systematic public health surveillance and more studies considering all potential confounding factors.

by the health authorities, such as Health Canada, and marketed.[6] Bioequivalence, involving comparability of pharmacokinetic profiles of 2 pharmaceutical products containing the same amount of the active ingredient and presenting the same galenic formulation, is required for homologation of new generic compounds.[6] In Canada, the standards for comparative bioavailability of generic and brand-name products used to demonstrate bioequivalence are (1) the area under the curve of the last quantifiable concentration and (2) the maximal concentration (C_{max}) after dosing. The 90% confidence interval (90% CI) of the relative mean of the area under the curve of the last quantifiable concentration and the relative mean of C_{max} (ratio only) should range within 80% and 125% to be considered bioequivalent.[6] These regulations are stricter for 9 narrow therapeutic index drugs in Canada and may vary across countries.

Doubts were raised in the literature regarding clinical equivalence of generic drugs after substitution versus their brand-name counterpart in several therapeutic fields.[7–17] A recent meta-analysis including studies of generic and brand-name cardiovascular drugs did not show a significant difference in terms of safety or tolerability between the 2 types of drug.[18] However, a systematic review of editorials addressing generic drug substitution in cardiology depicted a majority of negative views on clinical equivalence.[18] Most of population-based, time series analyses support generics commercialization but are only evaluating prescription rates or economical outcomes.[19–21] Three studies evaluating clinical outcomes after generics introduction with time series reported conflicting results.[13,22,23] Whether bioequivalence of generic drugs translates into clinical equivalence at a population level is unclear. The present study aimed to (1) characterize the entry of the generic angiotensin II receptor blockers (ARBs) analogs on the Canadian market and (2) evaluate the impact of generic ARBs commercialization on adverse events (any causes emergency room (ER) consultations or hospitalizations) in elderly patients in real-life conditions. We hypothesized that there would be a difference in rates of adverse events after generic ARBs commercialization compared with the period before their availability.

Methods

Source of Data

Data of this observational retrospective interrupted time series study was retrieved from the Quebec Integrated Chronic Disease Surveillance System (QICDSS).[24] The QICDSS is a twinning of 5 medico-administrative files held by the public health insurance board in Quebec, named *Régie de l'assurance maladie du Québec* (RAMQ) and the health ministry. Four of these files were used: the health insurance registry, hospitalizations, medical, and pharmaceutical services claims databases. Of note, public drug insurance is universal in Quebec, Canada, and ≈90% of citizens ≥65 years old were publicly insured in 2011 to 2012.[24,25] Data are linked by a unique anonymized identification number and are updated on a yearly basis. As of May 2017, data are available from January 1, 1996, to March 31, 2015. This study is part of the continuous chronic disease surveillance mandate granted to the National Public Health Institute of Quebec (*Institut national de santé publique du Québec;* INSPQ) by the provincial minister of health and social services. All surveillance activities of this mandate are approved by the provincial Ethics Committee of Public Health. No informed consent was required.

Study Drug and Exposure

A total of 3 brand-name ARBs and 16 generic analogs were studied. The ARBs drugs were losartan, valsartan, and candesartan, of all dosages, identified by their respective drug identification number in the pharmaceutical services claims database. All generic versions commercialized within 6 months of patent expiry were included in the study. Brand-name losartan[26] lost its patent in January 2012, and 8 generics versions were included in the analysis. Brand-name valsartan[27] and candesartan[28] lost their patent, respectively, in January and April 2011. It was followed by the commercialization of, respectively, 5 and 3 generic analogs included in the analysis. Exposure to generic or brand-name drugs was captured at an individual level, reflecting each patients' actual drug exposure for every single day of contribution to monthly cohorts. In other words, all included patients had an active claim of at least 1 day in the given month (Figure IA in the Data Supplement). Person-day exposure was calculated from the drug identification number, as well as the start date and duration of prescription dispensed from pharmaceutical claims in the database (Figure IA and IB in the Data Supplement). As a claim might be done before all pills from previous claim are used, exact generic drug start date for group attribution was corrected by continuous multiple interval measure of oversupply.[29] Continuous multiple interval measure of oversupply was calculated retrospectively, 4 months preceding the beginning of each series. Individual person-months contribution to the series were only recorded if patients had an active generic or brand-name drug claim in their possession (Figure IA in the Data Supplement); therefore, patients with no active drug claim were not contributing to the series. Each series were constituted of 36 open monthly cohorts. For example, a persistent patient could have contributed to the full series, while a nonpersistent patient contributed only during periods of usage (Figure IB in the Data Supplement). More details on monthly cohorts and exposures are available in the Data Supplement.

Study Periods for Interrupted Time Series

Study periods were determined by the date when the patent of each brand-name drug expired and generic analogs were marketed and available. Consequently, each drug has a different study time frame. The exact date when a patient claimed the first generic analog for the first time, for each brand-name drug, indicated the month when generics were commercialized. Interrupted time series[30] were constituted of all patients aged ≥66 years old users of losartan, valsartan, or candesartan who were observed for adverse events every month,

24 months before and 12 months after generics commercialization (36 transversal observations). Consequently, the number of person-months at risk varied monthly, giving no possibility to measure drug adherence or switches from brand to generics.

Adverse Events

Adverse events considered were any causes of ER consultations or hospitalizations. No specific diagnosis associated with adverse events was selected because of the wide range of nonspecific symptoms potentially leading to ER consultations or hospitalizations. With known different bioavailability for generic ARB drugs (as documented in generic drugs' product monographs), theoretical acute or delayed variations in efficacy are possible and may lead to adverse drug reactions (eg, dizziness, diarrhea, headache, coughing, hypotension) or lack of efficacy (hypertension or congestive heart failure, depending on the severity of the cases), potentially leading to ER consultations or hospitalizations.[26–28]

Statistical Analyses

Study Drugs

Proportions of utilization of brand-name/generic drugs of losartan, valsartan, and candesartan were calculated daily, from the moment of commercialization of generic analogs until the end of availability of information in the pharmaceutical services claims database (March 31, 2015). This was expressed graphically to represent market shares evolution for each drug after generics commercialization.

Interrupted Time Series and Segmented Regressions

Descriptive statistics of all relevant patients' characteristics were performed, including proportions, means, and standard deviations, as appropriate. Time series[30] were used to report crude monthly rates of adverse events, including ER consultations or hospitalizations, 24 months before ≤12 months after generics commercialization. These interrupted time series were represented graphically for all users and specifically for generics versus brand-name users after generics commercialization. Negative binomial segmented regression models, which generalize the Poisson regression models in the presence of overdispersion,[31] were performed to assess the difference in trends of adverse events after versus before arrival of generic analogs on the market for all users and according to generic and brand-name exposition. For each drug, there were 3 models, each modeling a type of adverse events (the rates of ER consultations, hospitalizations, and both) and 2 sets of these models. The first one evaluated the significance of sudden shift in rate level of adverse events and changes in trends after generics commercialization in the population. The second set of models included a specific variable identifying generic versus brand-name users in the population. Time series regression parameters and equations are presented in Table VI in the Data Supplement. A contrast test between regression coefficients was performed to compare statistical significance of the difference for generic versus brand-name users in terms of level of adverse events, the month of generics commercialization, and trends of adverse events in the year after generics commercialization, with differences in proportions and their respective 95% CIs. All regression models were verified for their respective validity assumptions (first-order autocorrelation and seasonality) by residuals graph examination and Durbin–Watson statistic.[30] A sensitivity analysis was performed using adjusted autoregressive models for the time series data, controlling for autocorrelation and seasonality. A second sensitivity analysis was performed without correction for continuous multiple interval measure of oversupply. Because it is not possible to adjust the coefficients of these models to account for potential confounding factors, a third sensitivity analysis was performed by stratification of each time series based on the number of cardiovascular comorbidities associated to the risk of adverse events, as detailed in the method section in the Data Supplement. Stratification of each time series based on the socioeconomic status was also performed, as well as a falsification analysis with specific versus nonspecific cardiovascular outcomes, as described in the Data Supplement. Results were interpreted against documented differences in bioavailability of generic and brand-name drugs (as per respective product monographs). The significance level was set at 5%. All analyses were performed with SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

Results

Proportions of utilization of generic analogs after patent expiration of brand name losartan, valsartan, and candesartan are presented in Figure IIA through IIC in the Data Supplement, respectively. There was a rapid increase of market shares for generic analogs once they became available for the population. Losartan generics reached 50% of market shares within 2 months, whereas it took 1 year for generic valsartan and candesartan analogs to reach 50% of respective market shares. The proportion of brand-name users 2 to 3 years after generics commercialization of losartan, valsartan, and candesartan falls under 5%.

Losartan, valsartan, and candesartan users who contributed in these times series were around 60% women, in average 76 to 77 years old with ≥3 cardiovascular comorbidities for more than a third of patients (Table 1). Among all of these ARB users, prevalence of hypertension was 84% to 88%; ischemic heart disease, 37% to 40%; heart failure, 13% to 15%; and diabetes mellitus, 29% to 33%. They were using in average 10 concomitant drugs.

Losartan

Brand name losartan lost its patent in January 2012, and the first prescription of generic losartan was claimed on March 15, 2012. There were 28 539 different losartan users who contributed between 15 288 and 17 765 persons-months during the 3-year study period (Figure III in the Data Supplement). There was a rate of 107 adverse events per 1000 person-months at risk at the beginning of the observation period (Figure [A]). The month when generics were commercialized, the observed rates of adverse events per 1000 person-months at risk were 114 for generic versus 104 for brand-name users. Interrupted time series analysis revealed an 8.0% increase of adverse events for generic users right after generics commercialization versus stability for brand-name users (0.5%), resulting in a difference of 7.5% (95% CI, −0.9% to 15.9; P=0.0643; Table 2). This immediate difference was explained by a change of ER rates for generic versus brand-name users (8.5% [95% CI, 0.0% to 17.0%]; P=0.04; Figure IVA and Table II in the Data Supplement). Concomitantly, hospitalizations were similarly reduced for both generic and brand-name users (−5.1% versus −5.6%, difference of 0.5% [95% CI, −13.0% to 14.0%]; P=0.9433). Trend of adverse events ≤1 year after generics commercialization was modestly affected in the population (both groups together, 0.6% [0.0%–1.3%]; P=0.06; Figure VA in the Data Supplement). Specifically for generic users, it was stable, while there was a decrease in adverse events for brand-name users (difference of 2.0% [0.7%–3.4%]; P=0.0033). This difference was explained by a modestly increasing trend of hospitalizations for generic users while a decreasing trend for brand-name users (1.2% versus −2.1%, difference of 3.3% [0.7%–5.9%]; P=0.0126). Regarding ER consultations, there was a decrease in rates for both groups, but it was more

Table 1. Characteristics of Losartan, Valsartan, and Candesartan Users During the 3-Year Study Period

	Drugs and Study Periods		
	Losartan (March 2010 to February 2013)	Valsartan (April 2009 to March 2012)	Candesartan (July 2009 to June 2012)
Characteristics			
Age, y	77	76	76
Women, %	62.8	59.6	61.0
Comorbidities			
All comorbidities, n	3.3±2.1	3.0±2.0	3.0±2.0
≥5 comorbidities, %	24.4	20.0	20.2
Cardiovascular comorbidities, n	2.5±1.6	2.3±1.6	2.3±1.6
≥3 cardiovascular comorbidities, %	39.5	34.5	35.1
Hypertension, %	87.5	84.0	86.9
Ischemic cardiomyopathy, %	40.3	36.6	36.6
Heart failure, %	14.8	12.6	13.0
Stroke, %	11.8	9.8	10.5
Cardiogenic shock, %	0.4	0.4	0.4
Diabetes mellitus, %	33.4	29.3	29.5
Cardiac arrhythmia, %	12.7	12.0	12.2
Acute pulmonary edema, %	1.0	0.9	0.9
Renal failure, %	12.7	10.7	11.6
Heart valves disease, %	6.5	6.1	6.3
Chronic pulmonary obstructive disease, %	23.4	22.5	21.9
Concomitant drugs			
Nonproprietary name, n	10.4±6.6	9.7±6.4	9.8±6.3
Socioeconomic status (lowest quintile is favored)			
Lowest quintile of social deprivation, %	15.6	15.6	15.2
Highest quintile of social deprivation, %	23.5	23.4	23.3
Lowest quintile of material deprivation, %	19.5	16.7	17.8
Highest quintile of material deprivation, %	21.5	22.5	21.0
Region of residence			
Urban (>1.5 million inhabitants), %	50.3	50.3	47.9
Rural (<10 000 inhabitants), %	19.9	19.9	19.6

Data are presented as proportions or mean±standard deviations.

pronounced for brand-name users (−0.2% versus −2.1%, difference of 1.9% [0.5%–3.2%]; P=0.0081). Similar and proportional results were found in sensitivity analysis (Figure VIA in the Data Supplement). One studied generic showed statistically different bioavailability features compared with brand-name drug[32] and was used by 8% of the studied population the year after generics commercialization.

Valsartan

Brand-name valsartan lost its patent in January 2011, and the first prescription of generic valsartan was claimed on April 20, 2011. There were 59 500 different valsartan users who contributed between 29 715 and 35 877 persons-months during the 3-year study period (Figure III in the Data Supplement). There was a rate of 104 adverse events per 1000 person-months at risk at the beginning of the observation period (Figure [B]). The month of generics commercialization, the observed rates of adverse events per 1000 person-months at risk were 133 for generic users versus 98 for brand-name users. Interrupted time series analysis revealed a 11.7% increase of adverse events for generic users right after generic commercialization versus a decrease for brand-name users (−5.4%, resulting in a difference of 17.1% [9.9%–24.3%]; P<0.0001; Table 3). Similar results were found when itemized for hospitalizations or ER consultations for generic versus brand-name users (Figure IVB and Table III in the Data Supplement). Trend of adverse events −1 year after generics commercialization was not affected in the population (both groups together: 0.0% [−0.7% to 0.6%];

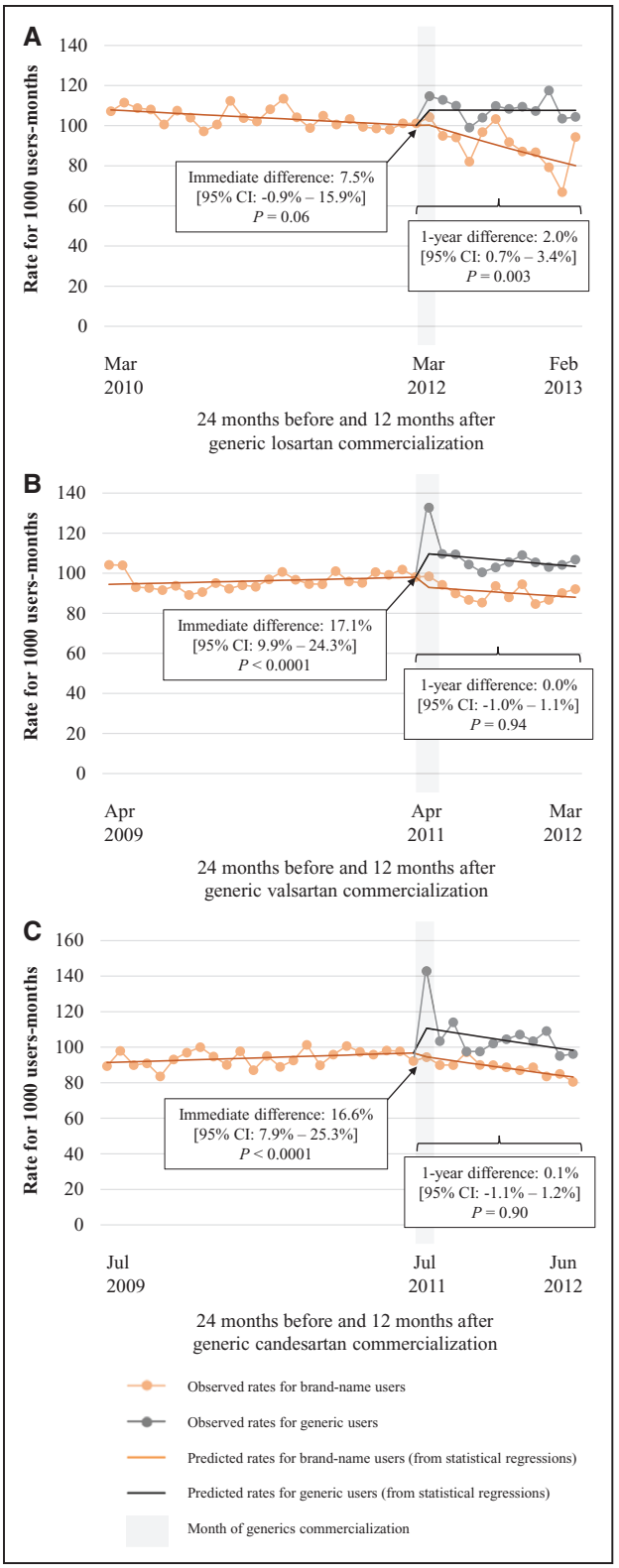


Figure. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of (**A**) 8 generic losartan analogs, (**B**) 5 generic valsartan analogs on the market, and (**C**) 3 generic candesartan analogs on the market. *P* value from contrast test: $e^{\text{coefficient-1(generics)}}$ vs $e^{\text{coefficient-1(brand-name)}}$. 95% CI indicates 95% confidence interval around the difference in proportions; and difference, difference in proportions of change in adverse events between generic and brand-name users.

P=0.9149; Figure VB in the Data Supplement). There were no statistical differences in trends of adverse events between groups (0.0% difference [−1.0% to 1.1%]; *P*=0.9405), even though observed rates were consistently higher for generic versus brand-name valsartan users. Similar and proportional results were found in sensitivity analysis, for patients at high and low cardiovascular risk (Figure VIB in the Data Supplement). One out of the 5 studied generics of valsartan showed statistically different bioavailability features compared with brand-name drug[33] but was used by only 4% of the studied population the year after generics commercialization.

Candesartan

Brand-name candesartan lost its patent in April 2011, and the first prescription of generic candesartan was claimed on July 6, 2011. There were 48 138 different candesartan users who contributed between 23 838 and 30 843 persons-months during the 3-year study period (Figure III in the Data Supplement). There was a rate of 89 adverse events per 1000 person-months at risk at the beginning of the observation period (Figure [C]). The month of generics commercialization, observed rates of adverse events were 143 for generic users versus 94 for brand-name users. Interrupted time series analysis revealed a 14.0% increase of adverse events for generic users right after generic commercialization versus a modest decrease for brand-name users (−2.6%, resulting in a difference of 16.6% [7.9%–25.3%]; *P*<0.0001; Table 4). Similar results were found when itemized for hospitalizations or ER consultations for generic versus brand-name users (Figure IVC and Table IV in the Data Supplement). Trend of adverse events ≤1 year after generics commercialization was modestly affected in the population (both groups together: −0.8% [−1.5% to −0.2%]; *P*=0.01; Figure VC in the Data Supplement). The year after generics commercialization, however, there were no statistical differences in trends of adverse events between groups (0.1% difference [−1.1% to 1.2%]; *P*=0.8989), even though observed rates were consistently higher for generic versus brand-name candesartan users. Similar and proportional results were found in sensitivity analysis, for patients at high and low cardiovascular risk (Figure VIC in the Data Supplement). All 3 studied generics showed statistically different bioavailability features compared with brand-name drug.[34–36]

Autocorrelation was evaluated by examining residuals and considering the Durbin–Watson test. Both were not significant. To confirm the absence of autocorrelation, a sensitivity analysis was performed using autoregressive models, and no difference was found versus our original analysis. Negative binomial segmented regression models were then considered valid. The second sensitivity analysis, without continuous multiple interval measure of oversupply, found similar results. As presented earlier, the last sensitivity analysis, with a stratification based on the number of cardiovascular comorbidities associated to the risk of adverse events, yielded similar results. Post hoc stratification for the socioeconomic status yielded similar results as well (data not shown). With highly labile curves and some low denominators, results from the falsification analysis revealed consistent differences in rates of specific cardiovascular outcomes between generic and brand-name users and no difference in rates of nonspecific cardiovascular outcomes for

Table 2. Estimation of Rates of Adverse Events 24 Months Before and 12 Months After Generic Losartan Commercialization

	All Users	Generics	Brand Name	Difference in Proportions	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	−0.3*	NA	−0.3†	NA	NA
Level change the month of generics commercialization (%, 24th month)	2.8	8.0†	0.5	7.5	−0.9 to 15.9
One-year trend change after generics commercialization (%, 24th to 36th month)	0.6	0.0	−2.0‡	2.0*	0.7 to 3.4

For interrupted time series analyzed by negative binomial segmented regression (% = $e^{coefficient-1}\times100$). All users include generic and brand-name users; generics include 8 different versions of generic losartan. 95% CI indicates 95% confidence interval around the difference in proportions; and NA, not applicable; difference in proportions of change in adverse events between generic and brand-name users.

*$P<0.01$.

†$P<0.05$.

‡$P<0.001$.

losartan and candesartan (Figures VIIA and VIIC in the Data Supplement).There was an increased rate of nonspecific cardiovascular outcomes for early generic valsartan users (Figure VIIB in the Data Supplement). However, this increase resulted in a nonstatistically significant difference issued from the segmented regression model (month of generic valsartan commercialization: 9.1% [−14.2% to 32.4%]; P=0.42; ≤1 year after: 0.6% [−25.6% to 26.9%]; P=0.8).

Discussion

This study examined the clinical and populational impact of generics commercialization of 3 ARBs compounds: losartan, valsartan, and candesartan. For generic users, we observed differences in rates of adverse events after generics commercialization using time series analysis. To our knowledge, this is the first ecological study assessing clinical outcomes with time series analysis after generics commercialization using a specific variable distinguishing between generic and brand-name users.

As expected, a rapid shift in market shares in favor of generic drugs was observed. The last brand-name ARBs to lose its patent, in our study, was losartan in 2012. It reached 50% of market shares in 2 months, while it took 1 year for generics valsartan and candesartan. This could hypothetically be explained by better confidence of pharmacists to switch patients to a generic formulation because they did not notice major individual problems during previous experiences (valsartan and candesartan). Prescribers were maybe more confident too, for the same reasons, and stopped using the "Do not substitute" writing on prescription labels. Because most of brand-name users will be switched to a generic analog within 2 to 3 years, we felt that long-term surveillance of adverse events is justified because the usage of generic drugs has not been tested for clinical equivalence (only bioequivalence versus brand-name drug). Losartan, valsartan, and candesartan lost their patent in January 2012, January 2011, and April 2011, respectively. There was a delay of 2 to 3 months between patent loss and the exact date when a patient claimed the first generic analog for the first time. This could be explained by administrative delay for registration of those new generic drugs on the provincial formulary as for drug coverage within the public plan.[37]

For losartan, valsartan, and candesartan, we observed a clinically significant increase of adverse events the month of generics commercialization for generic users. Increases were clinically significant for all studied drugs (losartan, 8.0%; valsartan, 11.7%; and candesartan, 14.0%) and significantly higher versus brand-name for valsartan and candesartan ($P<0.0001$). In addition, for valsartan and candesartan, we observed simultaneous decreases in adverse events rate for brand-name users. A statistically significant polarity was also observed for losartan in the trend of all adverse events ≤1 year after generics commercialization. These results are in contrast from Paterson et al,[13] who did not observe an increase in hospitalizations for major hemorrhage or cerebral thromboembolism after the implementation of a generic warfarin substitution policy in Ontario. However, time series were not stratified for generic and brand-name users and were not conducted for at least 12 months after policy implementation.[30] In another study including 15 different drugs of various therapeutic indications, a statistically meaningful increase in the number of reported adverse events was observed after generic

Table 3. Estimation of Rates of Adverse Events 24 Months Before and 12 Months After Generic Valsartan Commercialization

	All Users	Generics	Brand Name	Difference in Proportions	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	0.2	NA	0.2	NA	NA
Level change the month of generics commercialization (%, 24th month)	−1.6	11.7*	−5.4†	17.1‡	9.9 to 24.3
One-year trend change after generics commercialization (%, 24th to 36th month)	0.0	−0.5	−0.5	0.0	−1.0 to 1.1

For interrupted time series analyzed by negative binomial segmented regression (%=$e^{coefficient-1}\times100$). All users include generic and brand-name users; generics include 5 different versions of generic valsartan. 95% CI indicates 95% confidence interval around the difference in proportions; NA, not applicable; difference in proportions of change in adverse events between generic and brand-name users.

*$P<0.001$.

†$P<0.05$.

‡$P<0.0001$.

Table 4. Estimation of Rates of Adverse Events 24 Months Before and 12 Months After Generic Candesartan Commercialization

	All Users	Generics	Brand Name	Difference in Proportions	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	0.3*	NA	0.3*	NA	NA
Level change the month of generics commercialization (%, 24th month)	−0.8	14.0†	−2.6	16.6‡	7.9 to 25.3
One year trend change after generics commercialization (%, 24th to 36th month)	−0.8*	−1.1*	−1.1§	0.1	−1.1 to 1.2

For interrupted time series analyzed by negative binomial segmented regression (%=$e^{coefficient-1}\times100$). All users include generic and brand-name users; generics include 3 different versions of generic candesartan. 95% CI indicates 95% confidence interval around the difference in proportions; and NA, not applicable; difference in proportions of change in adverse events between generic and brand-name users.

*$P<0.05$.

†$P<0.001$.

‡$P<0.0001$.

§$P<0.01$.

introduction on the market for 7 of these drugs after negative binomial regression analysis.[22] Again, results were not stratified for generic versus brand-name users, just like in another recently published article,[23] who revealed no difference in adverse events after bioequivalence approval of particular products in United States. Coherently, our nonstratified analyses revealed limited impact of generics commercialization for all users (generic and brand-name users together).

The immediate increase of adverse events observed after 3 different generic drugs commercialization could hypothetically be explained by differences between drugs. Homologation standards require bioequivalence between brand-name and generic versions. A 20% variability for some pharmacokinetic parameters is accepted for most oral generic analogs[6] to be considered bioequivalent. In the product monographs, bioavailability features of 5 out of the 16 studied generic ARBs were statistically different from the brand-name counterpart.[32–36] In our study, patients could have been substituted to a generic version that is 6% to 21% different from the brand-name version that was used. Such a substitution to a more or less potent and effective version could have consistently happened for candesartan,[34–36] and interestingly, this is also the drug with the highest effect on adverse events right after generics commercialization. The increase in adverse events between generic and brand-name users could also be explained by differences in users' characteristics. Post hoc descriptive analysis (Table V in the Data Supplement) were performed to compare characteristics of generic versus brand-name users the first 2 months after generics commercialization. As expected, material and social deprivations are discordant characteristics between early generic versus concomitant brand-name users. Socially and mostly materially deprived patients tended to go on generics first, once available, which is coherent because generics are less expensive. However, it should be reminded that public drug coverage is universal in Quebec, Canada, especially for citizens ≥65 years old.[24,25] Therefore, they only pay out a fraction of the drug's full price, either on brand-name or generics. Furthermore, copayment is minimal for those with low income. Along with this universal system, patients do not need to pay out of the pocket for physician visits, ER consultations, or hospitalizations. Another disparity between early generic users versus brand-name users the first 2 months of generics commercialization is the region of residence. Nonurban areas (everywhere in Quebec except the urban one with >1.5 million inhabitants) and early generic usage are associated. We think this could be because of (1) commercial practices (lower sales representativeness of brand-name drug in pharmacies and doctors' office in nonurban areas), and (2) different disparities in material deprivation affecting the propensity to be switched to a generic version. In any case, even with social and material deprivation disparities, the age and number of comorbidities speak for themselves: clinical differences are minimal. Our results are further supported by our third sensitivity analysis (stratification for patients at high and low risk of adverse events based on the number of cardiovascular comorbidities and socioeconomic status), which yielded similar results. The falsification analysis revealed variable but potentially interesting results (Figure VIIA through VIIC in the Data Supplement). In line with our a priori hypothesis, we found higher rates of specific cardiovascular adverse events (or specific ARBs-related outcomes) for all studied drugs and no difference for nonspecific outcomes for generic users. Even if differences in rates of nonspecific adverse events were visually observed for generic valsartan users the month of generic commercialization, this was not statistically significant. This difference may be explained in part because this is the group with the highest denominator (even though low) the month of generic commercialization (299 generic valsartan users-month versus 173 generic candesartan users-month versus 113 generic losartan users-month). As previously mentioned, time series curves were highly labile in falsification analysis. Therefore, those results must be interpreted cautiously. Time series and statistical analyses were highly limited because of lack of power at many points in time, variable denominators because of drug switches, and possibly insensitive coding of each specific diagnosis.[38]

The increase in adverse events is highest the first month after generic commercialization and is mitigated after, but some differences persist as rates of adverse events are consistently higher for generic users. The observed excess risk could hypothetically be the reflection of an acute response to bioequivalent, but not identical, generic drugs substitutions for first generics users, inducing acute adverse drug reactions, or lack of efficacy. The attenuation the following months could hypothetically be because of dilution of incident switchers among prevalent generic users, depletion of susceptible generic users (who could stop the drug or change brand),[39] or dosage adjustments for generic drugs users. Reducing trends

of adverse events for brand-name users only after generics commercialization should be interpreted cautiously (mostly observed in high cardiovascular risk patients). Because the way segmented regressions are constructed, the 1-year trend is affected by the intervention point estimate (being the month of generic commercialization in our study) to suit the observed data. Therefore, for interpretation purposes, the focus should remain on differences between generic and brand-name users (level change and trends). Either way, these important results merit further attention through systematic public health surveillance and more studies considering all potential confounding factors.

Study Limitations and Strengths

Unfortunately, even though we considered many sensitivity analyses, this type of study does not allow to control for individual-level variations or covariates without tangibly affecting the statistical power.[30] A potential cofounding variable that could over or underestimate the differences in proportion of adverse events after generic commercialization is the fact that concomitant pharmacological changes were not considered in this study. As well, another limitation inherent to medico-administrative databases is the lack of clinical data. Even though hospitalizations and pharmaceuticals claims databases are considered highly reliable,[38,40,41] we may overestimate or underestimate our findings. This ecological study was not intended to evaluate outcomes after intergenerics substitutions (eg, from generic A to generic B), interlots substitution of a same drug (eg, from lots A to lots B of brand-name losartan), to compare drug performance, neither controlling for other potential confounders. A retrospective cohort study with survival analysis would be pertinent to compare the time-to-event between individuals exposed to generic substitution and those using only the brand-name drug. This would offer the opportunity to control for many potential confounding variables or to create propensity-matched cohort by using an appropriate propensity score. Nevertheless, time series designs are known to be among the strongest designs to evaluate intervention effect in the population (ie, policy changes at national level) when randomized controlled trials are not possible.[30] Threat to internal validity are prevented by the method of segmented regression analysis, implying exactly 24 assessments of the monthly rate of adverse events before and 12 assessments after commercialization of generics for each model and controlling for preexisting trend.

Conclusions

In this time series analysis, there seems to be an increase of ER consultations and hospitalizations after generics commercialization among generic users for 3 antihypertensive drugs of the same class. The increase was more pronounced for candesartan, which is the studied drug with the largest difference in comparative bioavailability studies. Along with bioavailability differences between generic and brand-name drugs, some differences in user's characteristics could partly explain our findings. A study evaluating the time-to-event between exposed to generics substitution compared with continuous users of brand-name drugs and controlled for several potential confounders would be required because this could have an impact on public health and policies. Until then, this situation merits further attention. Systematic public health surveillance with accurate pharmacovigilance reporting to health authority would contribute to the safety of generic and brand-name drugs usage in real-life conditions.

Acknowledgments

This study was conducted at the National Public Health Institute of Quebec (INSPQ) as part of the continuous chronic disease surveillance mandate granted by the provincial minister of health and social services. Jacinthe Leclerc is recipient of a studentship from the Ordre des infirmières et infirmiers du Québec (Programme MELS-Universités). Dr Poirier is a senior clinical researcher of the Fonds de recherche du Québec-Santé (FRQ-S). Dr Guénette holds a Junior-1 clinical researcher salary award from the FRQ-S in partnership with the Société québécoise d'hypertension artérielle (SQHA).

Sources of Funding

There was no funding for this study as this project is part of the continuous chronic disease surveillance mandate in Quebec, Canada.

Disclosures

Jacinthe Leclerc is a regular adjunct professor at the Université du Québec à Trois-Rivières and received, in 2015–2016, a studentship from a pharmaceutical company, AbbVie. Jacinthe Leclerc was an employee of Novartis Pharmaceuticals Canada Inc. at the beginning of this project and until June 2015. AbbVie and Novartis Pharmaceuticals Canada have no regard/power in decisions made through this project. Dr Poirier has received honorary for continuing medical education/consultants/experts event from Abbott Vascular, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, NovoNordisk, Pfizer, Roche, Sanofi-Aventis, Servier, and Valeant. The other authors report no conflicts.

References

1. Johansen ME, Richardson C. Estimation of potential savings through therapeutic substitution. *JAMA Intern Med*. 2016;176:769–775. doi: 10.1001/jamainternmed.2016.1704.
2. Gumbs PD, Verschuren WM, Souverein PC, Mantel-Teeuwisse AK, de Wit GA, de Boer A, Klungel OH. Society already achieves economic benefits from generic substitution but fails to do the same for therapeutic substitution. *Br J Clin Pharmacol*. 2007;64:680–685. doi: 10.1111/j.1365-2125.2007.02958.x.
3. Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997-2000. *Ann Intern Med*. 2005;142:891–897.
4. Fischer MA, Avorn J. Economic implications of evidence-based prescribing for hypertension: can better care cost less? *JAMA*. 2004;291:1850–1856. doi: 10.1001/jama.291.15.1850.
5. Gouvernement du Québec. Mesure d'économie concernant les médicaments - Nouvelles règles concernant le recours à la mention ne pas substituer. 2015. www.msss.gouv.qc.ca/documentation/salle-de-presse/ficheCommunique.php?id=878. Accessed Septembre 9, 2016.
6. Santé Canada. Ligne directrice - Normes en matière d'études de biodisponibilités comparatives: Formes pharmaceutiques de médicaments à effets systémiques. *Médicaments et produits de santé* 2012. https://www.canada.ca/fr/sante-canada/services/medicaments-produits-sante/medicaments/demandes-presentations/lignes-directrices/biodisponibilite-bioequivalence/normes-matiere-etudes-biodisponibilite-comparatives-formes-pharmaceutiques-medicaments-effets-systemiques.html. Accessed February 6, 2017
7. LeLorier J, Duh MS, Paradis PE, Lefebvre P, Weiner J, Manjunath R, Sheehy O. Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. *Neurology*. 2008;70(22 pt 2):2179–2186. doi: 10.1212/01.wnl.0000313154.55518.25.
8. Kluznik JC, Walbek NH, Farnsworth MG, Melstrom K. Clinical effects of a randomized switch of patients from clozaril to generic clozapine. *J Clin Psychiatry*. 2001;62(suppl 5):14–17; discussion 23.

9. Molnar AO, Fergusson D, Tsampalieros AK, Bennett A, Fergusson N, Ramsay T, Knoll GA. Generic immunosuppression in solid organ transplantation: systematic review and meta-analysis. *BMJ*. 2015;350:h3163.
10. Palylyk-Colwell E, Jamali F, Dryden W, Friesen E, Koven S, Mohamed I, Osmond B, Alessi-Severini S, Sheldon L, Sheldon R, Tam Y, Tsuyuki R, Zhanel G. Bioequivalence and interchangeability of narrow therapeutic range drugs. Canadian Society for Pharmaceutical Sciences discussion. *J Pharm Pharm Sci*. 1998;1:2–7.
11. Nardi R, Masina M, Cioni G, Leandri P, Zuccheri P. Generic - Equivalent drugs use in internal and general medicine patients: Distrust, confusion, lack of certainties or of knowledge? Part 2. Misconceptions, doubts and critical aspects when using generic drugs in the real world. *Ital J Med*. 2014;8:88–98.
12. Ghate SR, Biskupiak JE, Ye X, Hagan M, Kwong WJ, Fox ES, Brixner DI. Hemorrhagic and thrombotic events associated with generic substitution of warfarin in patients with atrial fibrillation: a retrospective analysis. *Ann Pharmacother*. 2011;45:701–712. doi: 10.1345/aph.1P593.
13. Paterson JM, Mamdani M, Juurlink DN, Naglie G, Laupacis A, Stukel TA. Clinical consequences of generic warfarin substitution: an ecological study. *JAMA*. 2006;296:1969–1972. doi: 10.1001/jama.296.16.1969-b.
14. Kwong WJ, Kamat S, Fang C. Resource use and cost implications of switching among warfarin formulations in atrial fibrillation patients. *Ann Pharmacother*. 2012;46:1609–1616. doi: 10.1345/aph.1Q472.
15. van den Bergh JP, Bouts ME, van der Veer E, van der Velde RY, Janssen MJ, Geusens PP, Winkens B, Oldenhof NJ, van Geel TA. Comparing tolerability and efficacy of generic versus brand alendronate: a randomized clinical study in postmenopausal women with a recent fracture. *PLoS One*. 2013;8:e78153. doi: 10.1371/journal.pone.0078153.
16. Ringe JD, Möller G. Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. *Rheumatol Int*. 2009;30:213–221. doi: 10.1007/s00296-009-0940-5.
17. Madian AG, Panigrahi A, Perera MA, Pinto N. Case report: Inability to achieve a therapeutic dose of tacrolimus in a pediatric allogeneic stem cell transplant patient after generic substitution. *BMC Pharmacol Toxicol*. 2014;15:69. doi: 10.1186/2050-6511-15-69.
18. Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA*. 2008;300:2514–2526. doi: 10.1001/jama.2008.758.
19. Godman B, Petzold M, Bennett K, Bennie M, Bucsics A, Finlayson AE, Martin A, Persson M, Piessnegger J, Raschi E, Simoens S, Zara C, Barbui C. Can authorities appreciably enhance the prescribing of oral generic risperidone to conserve resources? Findings from across Europe and their implications. *BMC Med*. 2014;12:98. doi: 10.1186/1741-7015-12-98.
20. Hesse U, Godman B, Petzold M, Martin A, Malmström RE. Impact of delisting ARBs, apart from losartan, on ARB utilisation patterns in Denmark: implications for other countries. *Appl Health Econ Health Policy*. 2013;11:677–685. doi: 10.1007/s40258-013-0059-4.
21. Stenner SP, Chen Q, Johnson KB. Impact of generic substitution decision support on electronic prescribing behavior. *J Am Med Inform Assoc*. 2010;17:681–688. doi: 10.1136/jamia.2009.002568.
22. Hellström J, Rudholm N. Side effects of generic competition? *Eur J Health Econ*. 2004;5:203–208. doi: 10.1007/s10198-004-0234-5.
23. Gagne JJ, Polinski JM, Jiang W, Dutcher SK, Xie J, Lii J, Fulchino LA, Kesselheim AS. Outcomes associated with generic drugs approved using product-specific determinations of therapeutic equivalence. *Drugs*. 2017;77:427–433. doi: 10.1007/s40265-017-0696-2.
24. Blais C, Jean S, Sirois C, Rochette L, Plante C, Larocque I, Doucet M, Ruel G, Simard M, Gamache P, Hamel D, St-Laurent D, Emond V. Quebec Integrated Chronic Disease Surveillance System (QICDSS), an innovative approach. *Chronic Dis Inj Can*. 2014;34:226–235.
25. Régie de l'assurance maladie du Québec. Assurance médicaments: admissibilité. http://www.ramq.gouv.qc.ca/fr/citoyens/assurance-medicaments/Pages/admissibilite.aspx. Accessed March 27, 2017
26. Merck Canada Inc. Monographie de produit COZAAR (losartan potassique). 2014. http://www.merck.com/product/home.html. Accessed September 9, 2016.
27. Novartis Pharmaceuticals Canada Inc. Monographie de produit DIOVAN (valsartan). 2015. www.ask.novartispharma.ca/download.htm?res=diovan_scrip_e.pdf&resTitleId=725. Accessed September 9, 2016.
28. AstraZeneca Canada Inc. Monographie ATACAND (candésartan cilexétil). 2016. http://www.astrazeneca.ca/fr/Medicines/fr-Products-AZ. Accessed September 9, 2016.
29. Morningstar BA, Sketris IS, Kephart GC, Sclar DA. Variation in pharmacy prescription refill adherence measures by type of oral antihyperglycaemic drug therapy in seniors in Nova Scotia, Canada. *J Clin Pharm Ther*. 2002;27:213–220.
30. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27:299–309.
31. Vittinghoff E. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*. New York: Springer; 2012:340.
32. Teva Canada Limitée. Monographie de produit Teva-Losartan (losartan). 2012. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Accessed May 10, 2016.
33. Ranbaxy Pharmaceuticals Canada Inc. Monographie de produit RAN-VALSARTAN (valsartan). 2015. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Accessed September 9, 2016.
34. Actavis Pharma Company. Product monograph Act Candesartan. 2014. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Accessed February 17, 2016
35. Apotex Inc. Monographie de produit APO-CANDESARTAN (candésartan). 2013. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Accessed May 10, 2016.
36. Sandoz Canada Inc. Monographie de produit SANDOZ CANDESARTAN (candésartan). 2016. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html. Accessed September 9, 2016.
37. Institut national d'excellence en santé et en services sociaux. Faire une demande d'inscription. 2016. https://www.inesss.qc.ca/activites/evaluation-des-medicaments/rendez-vous-des-fabricants/faire-une-demande-dinscription.html. Accessed August 7, 2017
38. Lambert L, Blais C, Hamel D, Brown K, Rinfret S, Cartier R, Giguère M, Carroll C, Beauchamp C, Bogaty P. Evaluation of care and surveillance of cardiovascular disease: can we trust medico-administrative hospital data? *Can J Cardiol*. 2012;28:162–168. doi: 10.1016/j.cjca.2011.10.005.
39. Strom BL, Kimmel SE, Hennessy S. *Textbook of Pharmacoepidemiology*. Chichester, West Sussex: John Willey and Sons Ltd; 2013.
40. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. *J Clin Epidemiol*. 2004;57:131–141. doi: 10.1016/S0895-4356(03)00246-4.
41. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol*. 1995;48:999–1009.

Impact of the Commercialization of Three Generic Angiotensin II Receptor Blockers on Adverse Events in Quebec, Canada: A Population-Based Time Series Analysis

Jacinthe Leclerc, Claudia Blais, Louis Rochette, Denis Hamel, Line Guénette and Paul Poirier

Circ Cardiovasc Qual Outcomes. 2017;10:
doi: 10.1161/CIRCOUTCOMES.117.003891
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713

SUPPLEMENTAL MATERIAL

Methods

Monthly cohorts and exposure

Exposure to generic or brand-name drugs were captured at an individual level, reflecting each patients' actual drug exposure for every single-day of contribution to monthly cohorts, either before or after generics commercialization (Figures S1a and S1b of this document). After generics commercialization, many patients remained on brand-name, while others switched on a generic version. Apart from random coding errors in medico-administrative files, there is very low probability of misclassification between generic and brand-name usage. Assessment of medication adherence was not possible, as time series design does not permit the follow up of individual patients through the 36-month period. However, patients were only contributing to time series if they had an active drug claim in their possession. Therefore, patients were not contributing during periods of non-persistence.

Statistical analyses for interrupted time series and segmented regressions

Descriptive statistics of all relevant patients' characteristics were performed, including proportions, means and standard deviations, as appropriate. Specifically, these characteristics included age, sex, number of comorbidities and detailed proportions of diagnoses, number of concomitant different drugs with active claim (defined as non-proprietary name), social and material deprivation status based on a validated method[1] and region of residence. As post-hoc analysis, characteristics of brand-name vs. early generic users were described.

We used negative binomial regression as crude rates of adverse events is the dependent variable[2]. The distribution of such rates generally follows a Poisson distribution rather than a Gaussian

distribution; frequency of rates are naturally negatively skewed and overdispersed[2, 3]. Negative binomial regression models are flexible enough to provide a best fit to such abnormally distributed data and include a specific variable to control for overdispersion. All regression models were constructed using the GENMOD procedure in SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA) and verified for their respective validity assumptions (1st order autocorrelation and seasonality) by residuals graphs examination and Durbin-Watson statistic. All others analyses were also performed with SAS Enterprise Guide 7.1, except for the first sensitivity analysis of this study. The latter was performed using adjusted autoregressive models for time series data using the ARIMA procedure only available in SAS/ETS (controlling for autocorrelation and seasonality). Details regarding model construction, variables, parameters, and equation regressions are presented in Table S6. As mentioned in the manuscript, a second sensitivity analysis was performed without correction for CMOS.

A third sensitivity analysis was performed by stratification of each time series based on the number of cardiovascular comorbidities associated to the risk of adverse events. Specifically, patients were classified as either being at high or low risk of adverse event based on the prevalence of the following comorbidities: hypertension, heart failure, ischemic cardiomyopathy, diabetes, chronic pulmonary obstructive disease, stroke, acute pulmonary edema, cardiac arrhythmias, chronic or acute renal failure, cardiogenic shock and heart valves disease. Patients at high risk where those with ≥ 3 cardiovascular comorbidities and patients at low risk had < 3 cardiovascular comorbidities. The cut-off of ≥ 3 was selected as this was including the upper third of patients with concomitant comorbidities (39.5% patients for losartan; 34.5% for valsartan and 35.1% for candesartan). Segmented regression models were conducted for all drugs and all adverse events as previously described. As well, our statistical program was validated by two different statisticians.

A final analysis (falsification analysis) was conducted using an *a priori* identified "tracer" outcome based on specific vs. non-specific adverse events possibly associated with ARBs treated patients (Table

S1). Segmented regression models were conducted for each drug, for specific and non-specific outcomes. Based on our research hypothesis, we did expect higher rates of specific cardiovascular adverse events (or specific ARBs-related outcomes), but no difference for non-specific outcomes, for generic users.

Figure S1a. Algorithm of exposure for generic and brand-name drug users constituting monthly time series cohorts

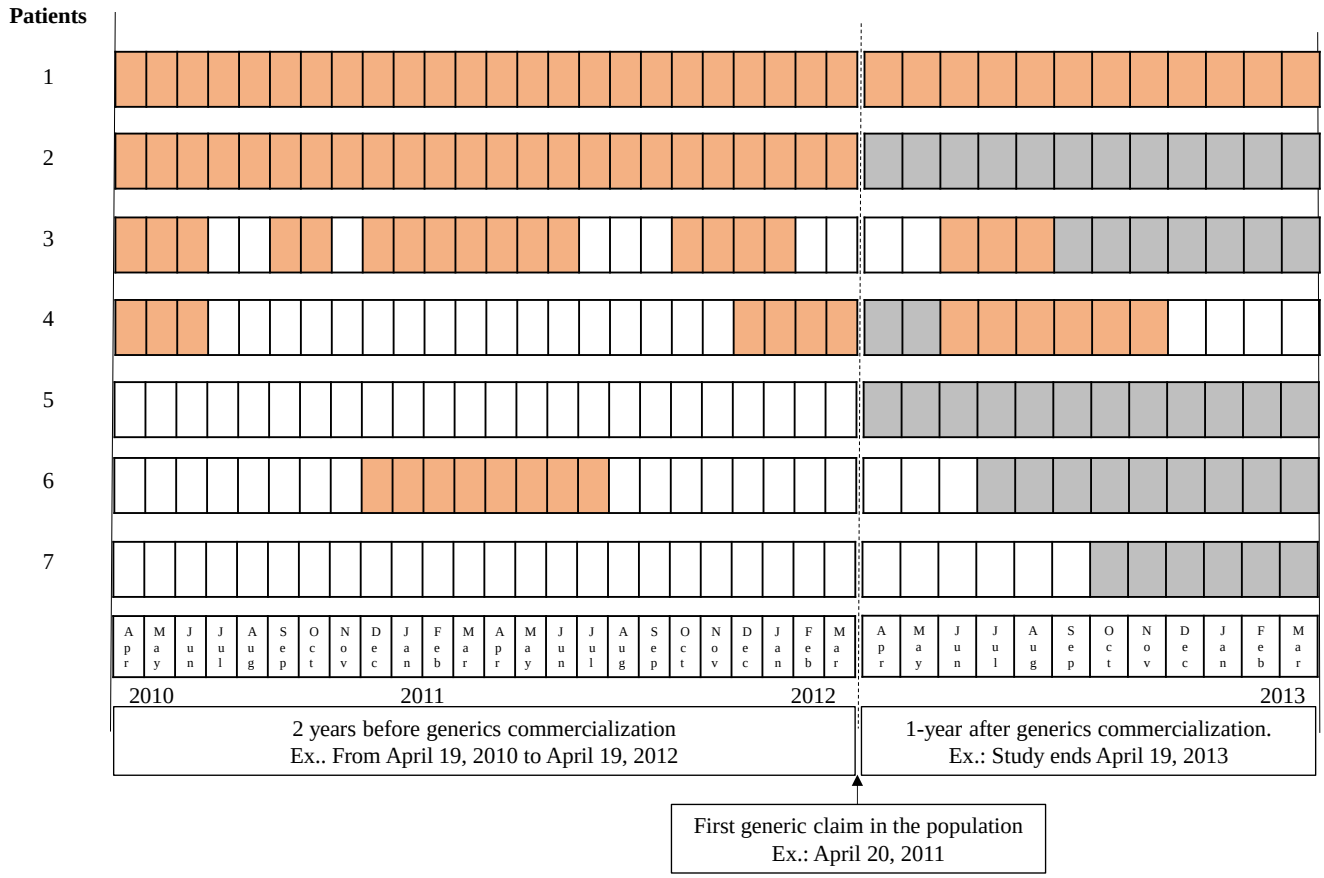


Figure legend for figure S1a

Person-months as user of a generic drug (active drug claim)

Person-months as users of the brand-name drug (active drug claim)

No active generic or brand-name drug claim (not contributing to the analysis)

Figure S1b. Illustration of an open monthly cohort (example of April 2011)

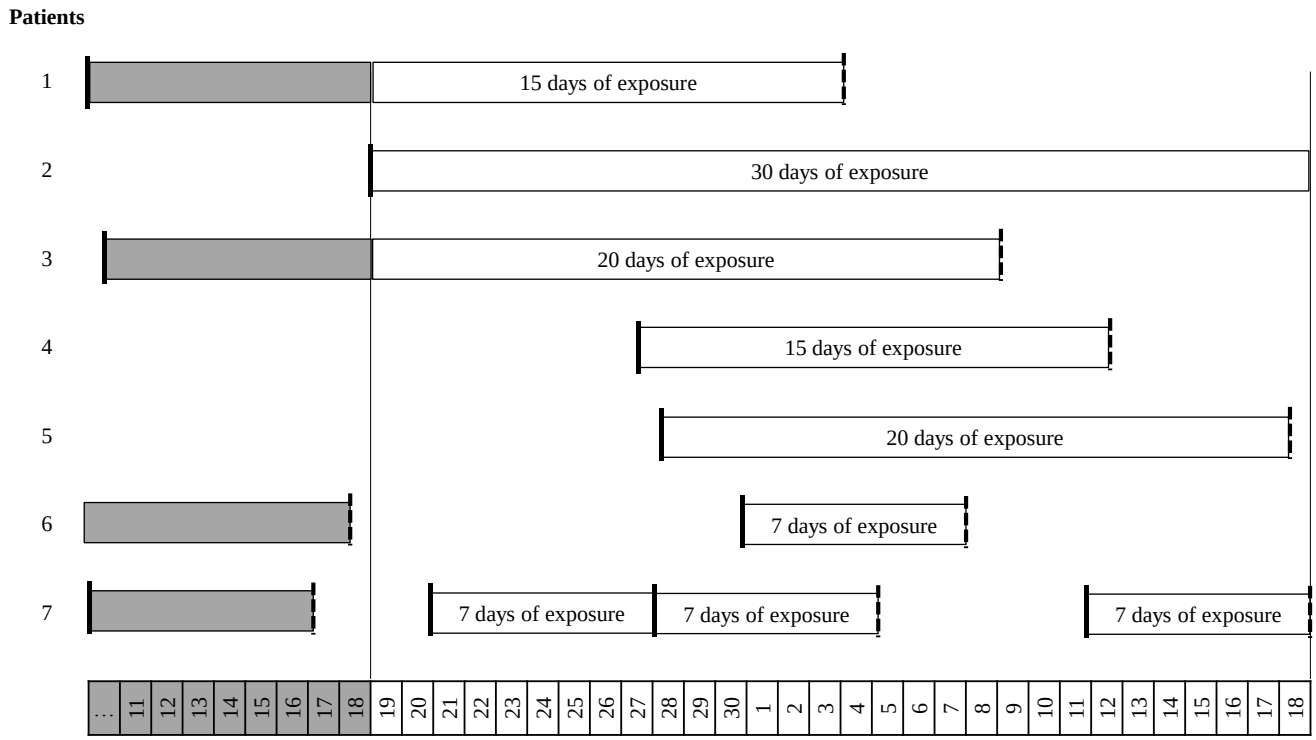


Figure Legend for Figure S1b

Start date of drug claim (Date dispensed)

End date of drug claim (Date dispensed + number of days dispensed)

Contributing to the monthly cohort of April 2011

Not contributing to the monthly cohort of April 2011

Figure S2a. Utilization of generic analogs after patent expiry of brand-name losartan

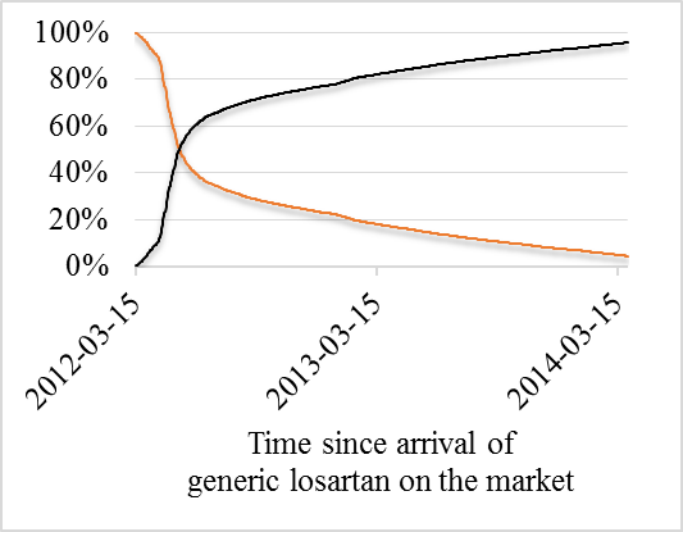


Figure S2b. Utilization of generic analogs after patent expiry of brand-name valsartan

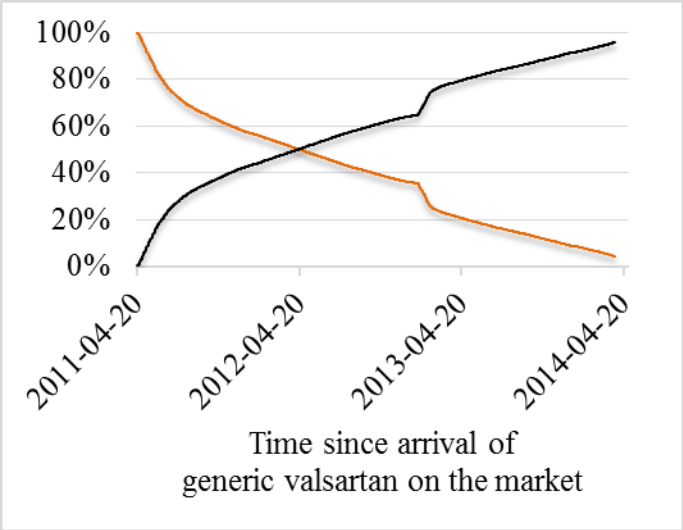


Figure S2c. Utilization of generic analogs after patent expiry of brand-name candesartan

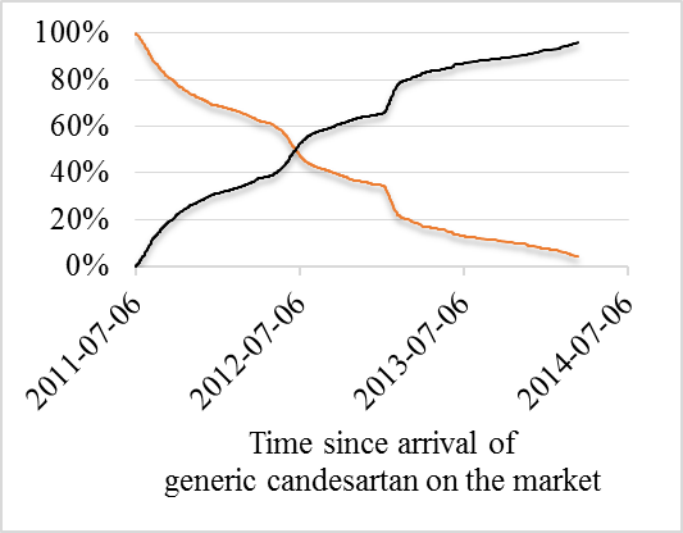


Figure Legend for Figures S2a, S2b and S2c.

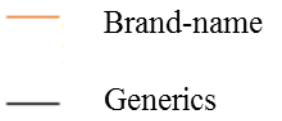


Figure S3. Flow chart of patients included in time series

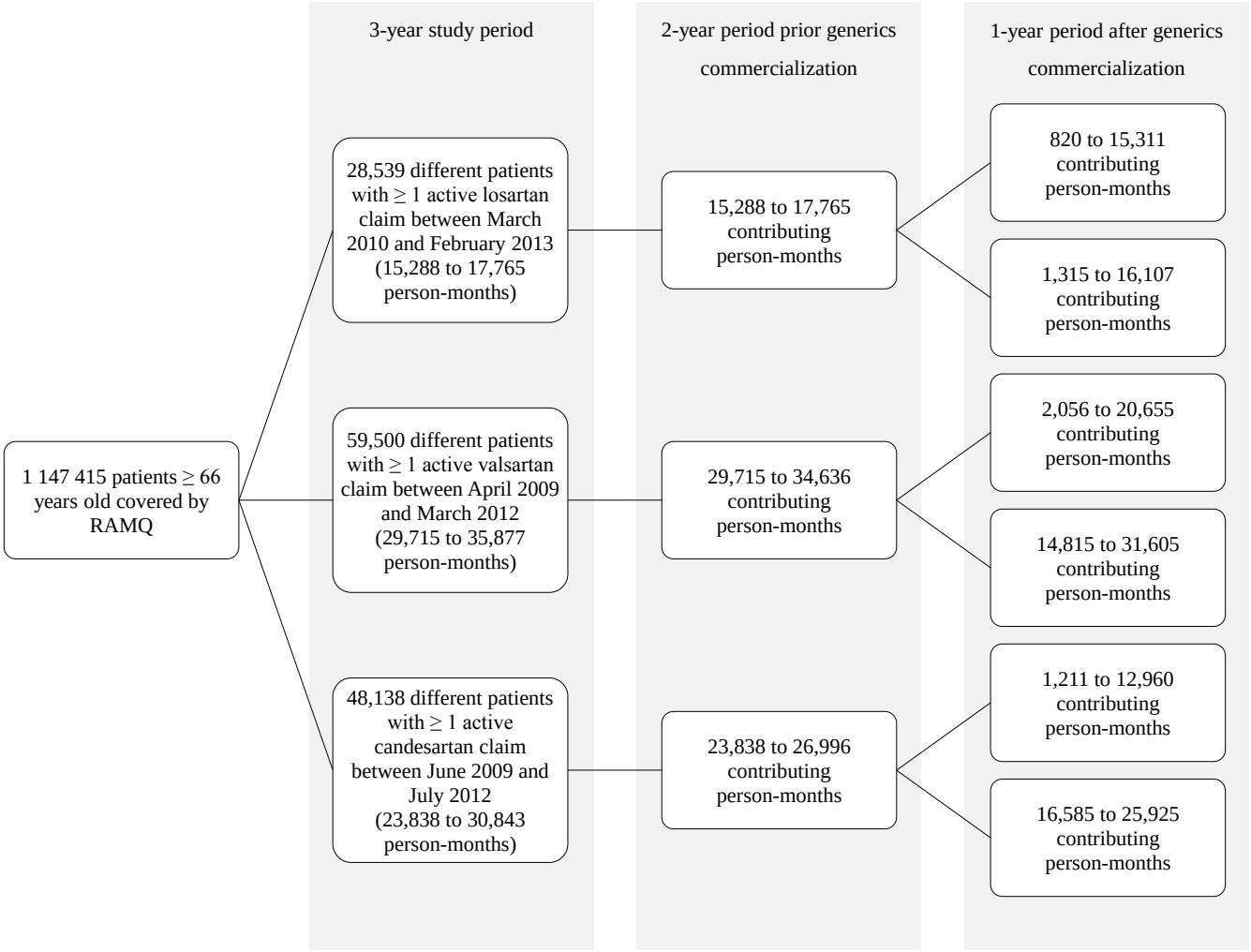


Figure Legend for Figure S3

RAMQ: Régie d'assurance maladie du Québec;
Only exposed patients with active drug claim were included in time series

Figure S4a. Interrupted time series analyses of hospitalizations and emergency room consultations 24 months before and 12 months after commercialization of 8 generic losartan analogs

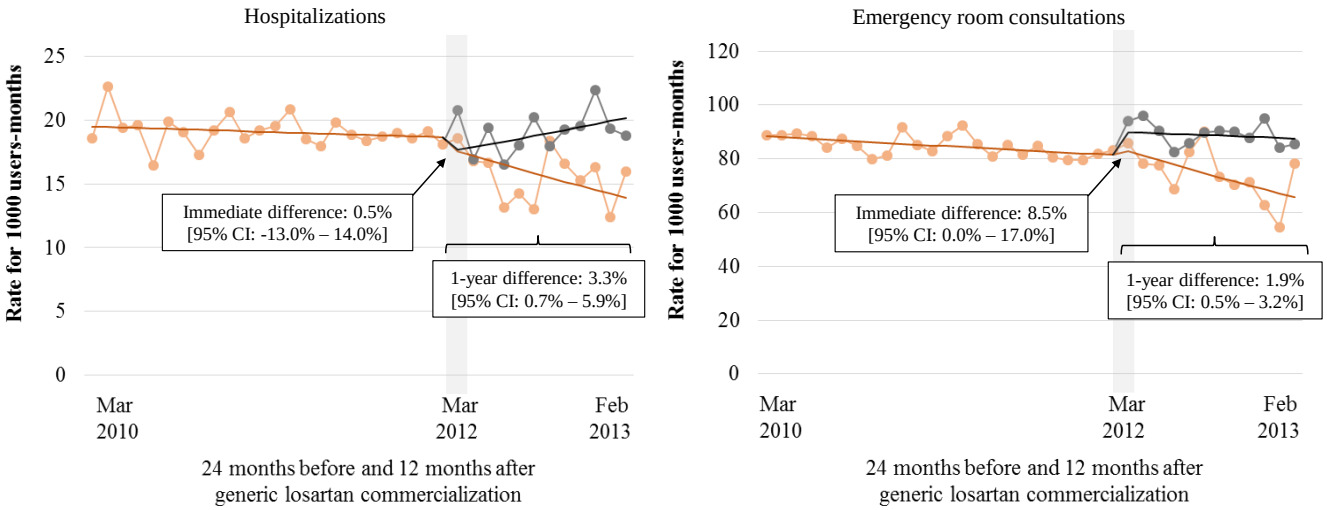


Figure S4b. Interrupted time series analysis of hospitalizations and emergency room consultations 24 months before and 12 months after commercialization of 5 generic valsartan analogs

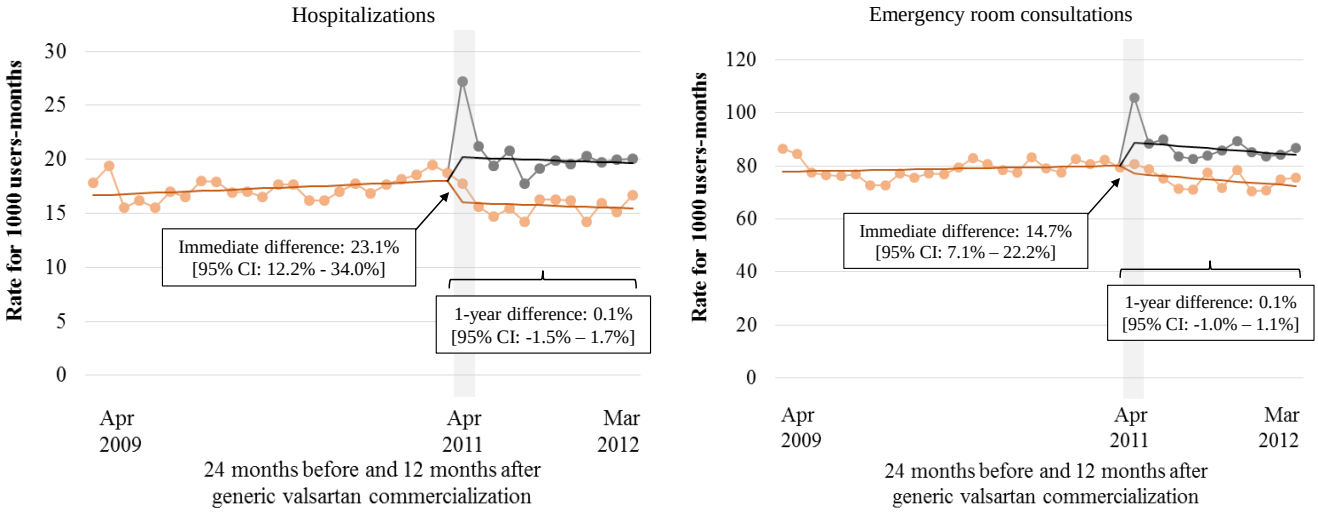


Figure S4c. Interrupted time series analysis of hospitalizations and emergency room consultations 24 months before and 12 months after commercialization of 3 generic candesartan analogs

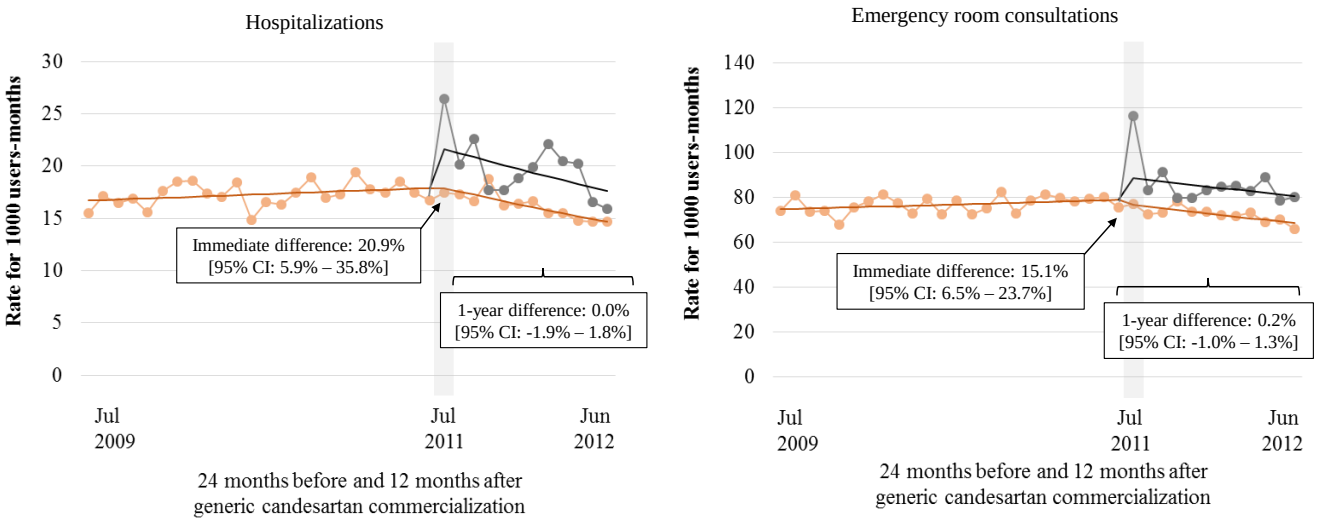


Figure Legend for Figures S4a, S4b and S4c

Observed rates for brand-name users

Observed rates for generic users

Predicted rates for brand-name users (from statistical regressions)

Predicted rates for generic users (from statistical regressions)

Month of generics commercialisation

Difference: difference in proportions of change in adverse events between generic and brand-name users

95% CI: 95% Confidence interval around the difference in proportions

Table S1. Specific and non-specific cardiovascular outcomes or adverse angiotensin II receptor blockers reactions

Adverse events categories	Specific outcomes	Codes	Non-specific outcomes	Codes
Hospitalizations (ICD-10-CA coding)	Coronary heart diseases	I200 to I255	Pneumonia	J120 to JI89
	Heart failure	I500 to I528	Bronchitis	J200 to J22
	Acute renal failure	N19, N170-N179	Chronic obstructive pulmonary disease	J440 and J449
	Syncope	R55	Senility	R54
	Hypertension	I100 to I13	Dementia	F03
	Hypotension (orthostatic or not)	I951 to I959	Tumor (benign or malignant)	C00 to C97
	Atrial fibrillation	I4800 to I4890		
Emergency room consultations (ICD-9 coding)	Coronary heart diseases, angina	40200 to 40291 4109 to 4149	Pneumonia	4800 to 4869
	Chest pain	7865 to 78659	Urinary tract infection	5959 and 5990
	Syncope	7802	Chronic obstructive pulmonary disease	4969
	Heart failure	4280 to 4289	Bronchitis	4660; 4909 to 4919
	Hypertension	4010 to 4019		
	Acute renal failure	5845 to 5869		
	Atrial fibrillation	4273		
	Hypotension (orthostatic or not)	4589 and 4580		

Table S2. Estimation of rates of hospitalizations and emergency room consultations 24 months before and 12 months after generics losartan commercialization.

	Hospitalizations				**Emergency room consultations**			
	Generics	Brand-name	DP	95% CI	Generics	Brand-name	DP	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	n/a	-0.2	n/a	n/a	n/a	-0.4†	n/a	n/a
Level change the month of generics commercialization (%, 24th month)	-5.1	-5.6	0.5	-13.0 – 14.0	10.7†	2.3	8.5*	0.0 – 17.0
One year trend change after generics commercialization (%, 24th to 36th month)	1.2	-2.1	3.3*	0.7 – 5.9	-0.2	-2.1‡	1.9†	0.5 – 3.2

Using models of segmented negative binomial regression; DP: difference in proportions; 95% CI: 95% Confidence interval around the difference in proportions; n/a: not applicable; * means $p < 0.05$; † means $p < 0.01$; ‡ means $p < 0.001$.

Table S3. Estimation of rates of hospitalizations and emergency room consultations 24 months before and 12 months after generics valsartan commercialization.

	Hospitalizations				**Emergency room consultations**			
	Generics	Brand-name	DP	95% CI	Generics	Brand-name	DP	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	n/a	0.3*	n/a	n/a	n/a	0.1	n/a	n/a
Level change the month of generics commercialization (%, 24th month)	11.5*	-11.6†	23.1‡	12.2 – 34.0	10.8†	-3.8	14.7‡	7.1 – 22.2
One year trend change after generics commercialization (%, 24th to 36th month)	-0.2	-0.3	0.1	-1.5 – 1.7	-0.5	-0.6	0.1	-1.0 – 1.1

Using models of segmented negative binomial regression; DP: difference in proportions; 95% CI: 95% Confidence interval around the difference in proportions; P value from contrast test: $e^{coefficient\text{-}1(generics)}$ vs. $e^{coefficient\text{-}1(brand\text{-}name)}$; * means $p < 0.05$; † means $p < 0.01$; ‡ means $p < 0.0001$.

Table S4. Estimation of rates of hospitalizations and emergency room consultations 24 months before and 12 months after generics candesartan commercialization.

	Hospitalizations				**Emergency room consultations**			
	Generics	Brand-name	DP	95% CI	Generics	Brand-name	DP	95% CI
Trend before generics commercialization (%, 1st to 23rd month)	n/a	0.3	n/a	n/a	n/a	0.2*	n/a	n/a
Level change the month of generics commercialization (%, 24th month)	20.5†	-0.3	20.2†	5.9 – 35.8	11.9†	-3.2	15.1‡	6.5 – 23.7
One year trend change after generics commercialization (%, 24th to 36th month)	-1.8*	-1.8‡	0.0	-1.8 – 1.9	-0.8	-1.0†	0.2	-1.0 – 1.3

Using models of segmented negative binomial regression; DP: difference in proportions; 95% CI: 95% Confidence interval around the difference in proportions; P value from contrast test: $e^{coefficient\text{-}1(generics)}$ vs. $e^{coefficient\text{-}1(brand\text{-}name)}$; * means $p < 0.05$; † means $p < 0.01$; ‡ means $p < 0.001$.

Figure S5a. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 8 generic losartan analogs for all users (generic and brand-name users: dotted line)

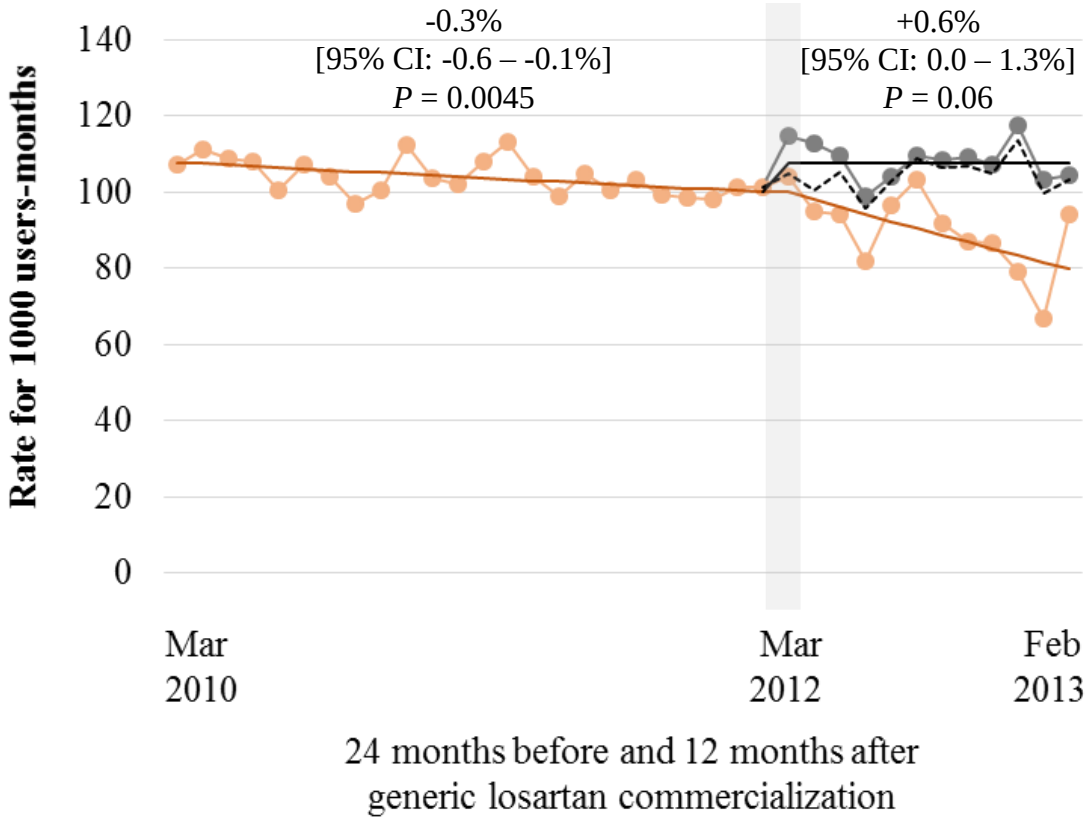


Figure S5b. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 5 generic valsartan analogs for all users (generic and brand-name users: dotted line)

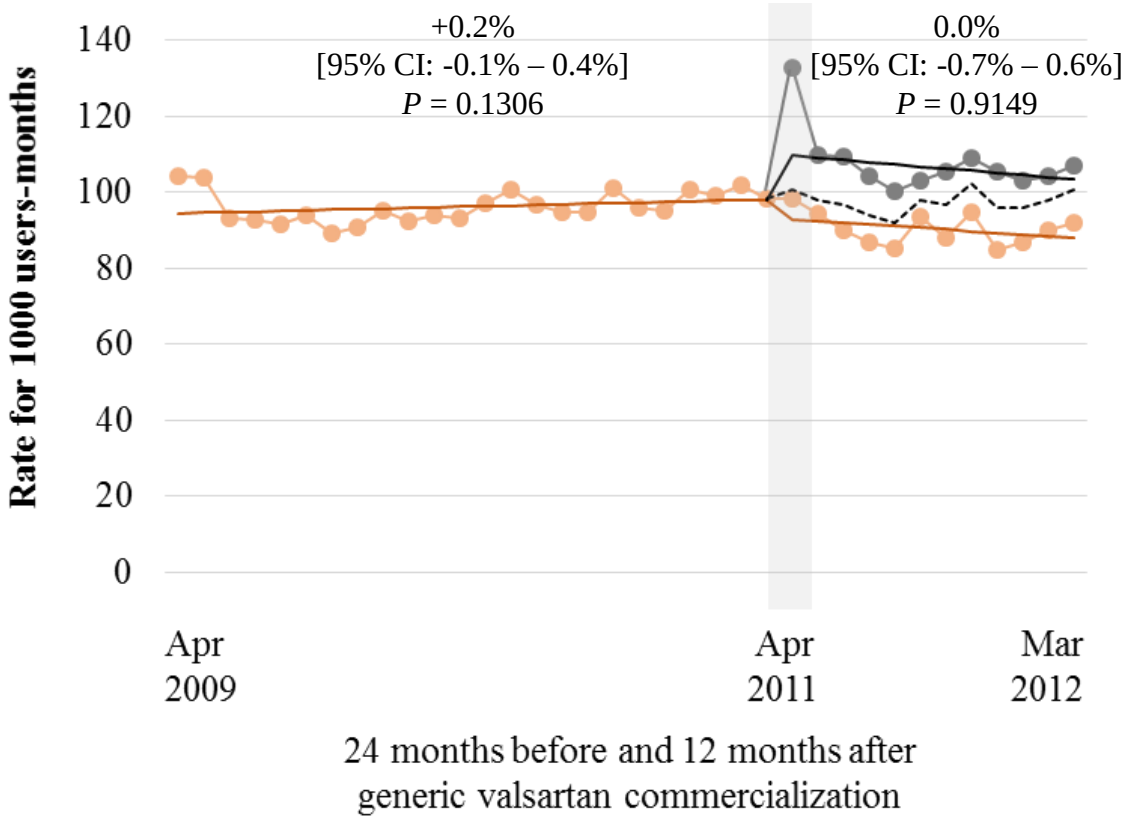


Figure S5c. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 3 generic candesartan analogs for all users (generic and brand-name users: dotted line)

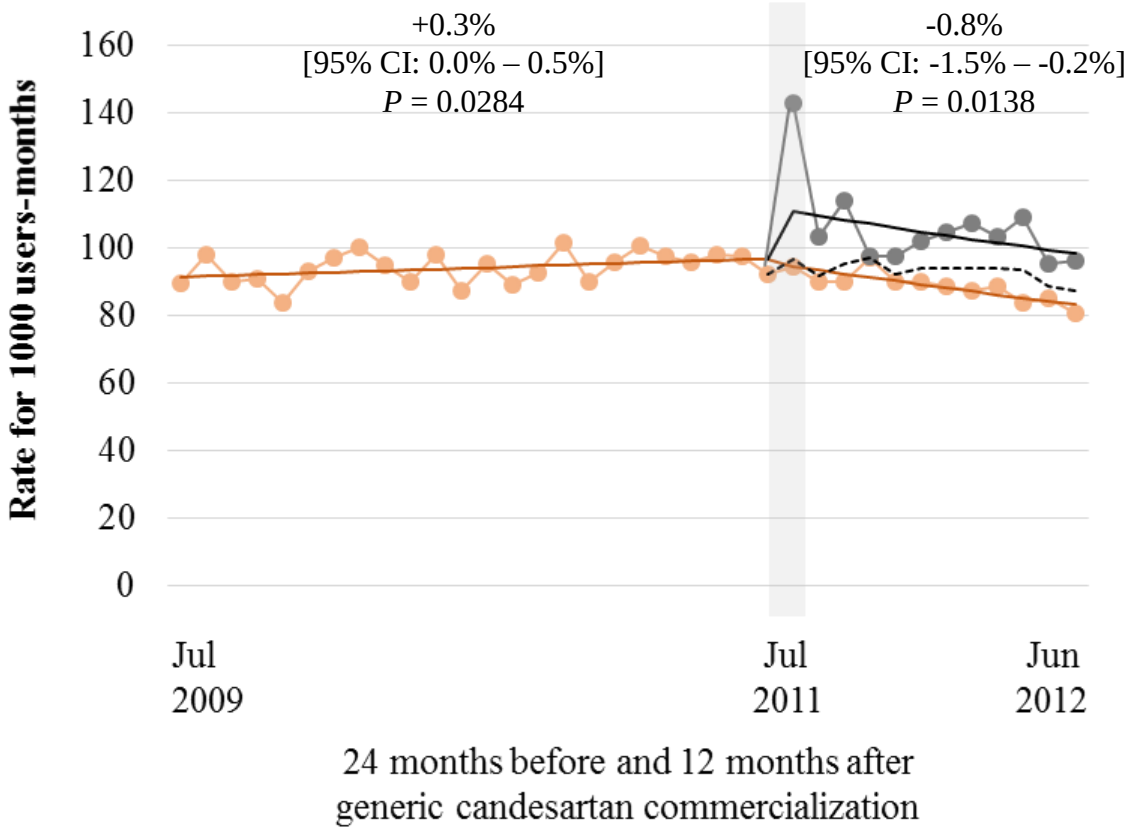
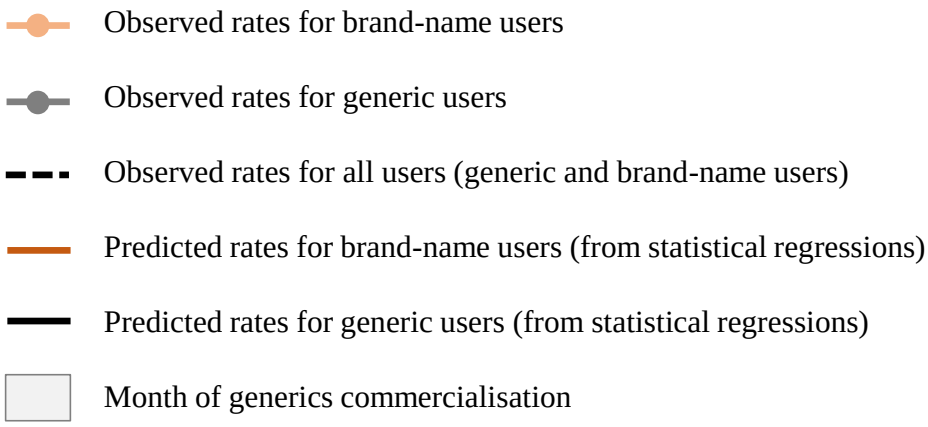


Figure Legend for Figures S5a, S5b and S5c



95% CI: 95% Confidence interval around the difference in proportions

Figure S6a. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 8 generic losartan analogs stratified for risk of adverse events

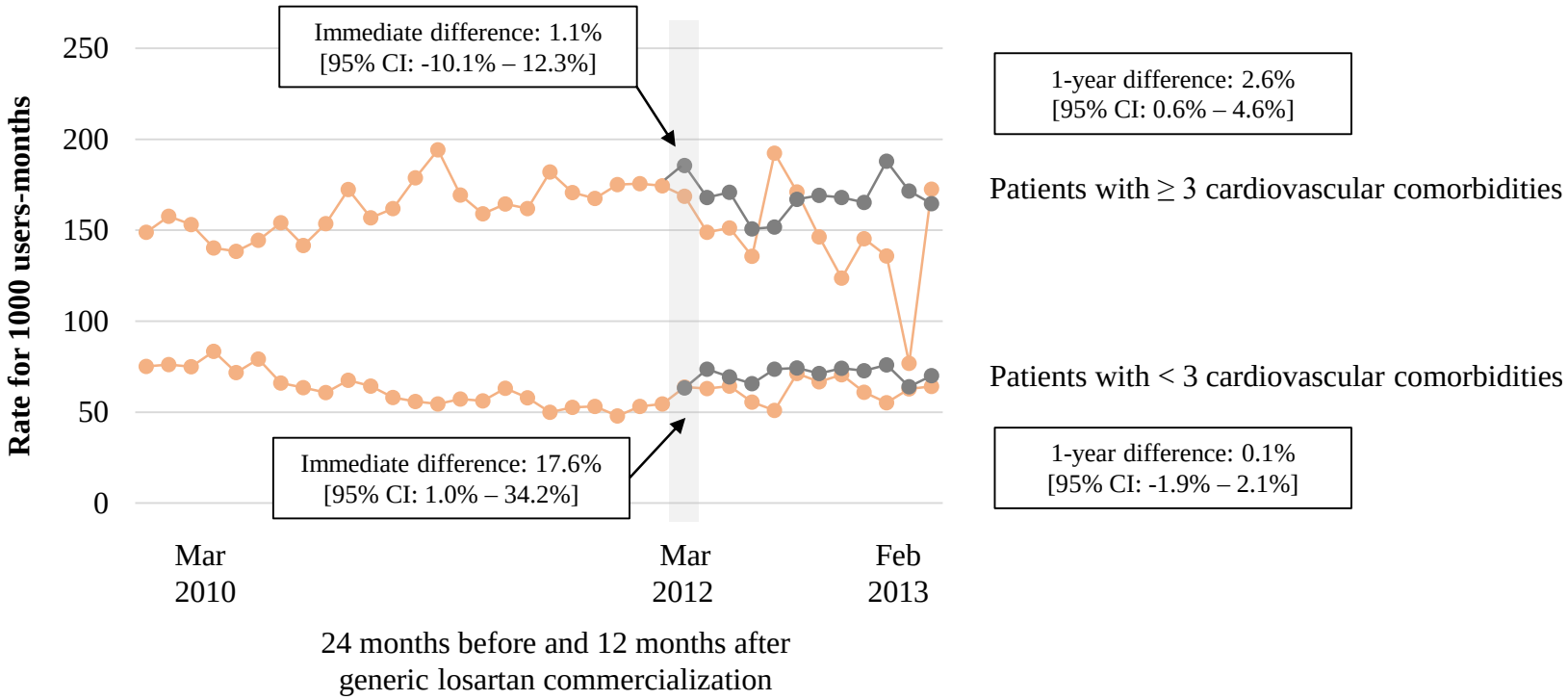


Figure S6b. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 5 generic valsartan analogs stratified for risk of adverse events

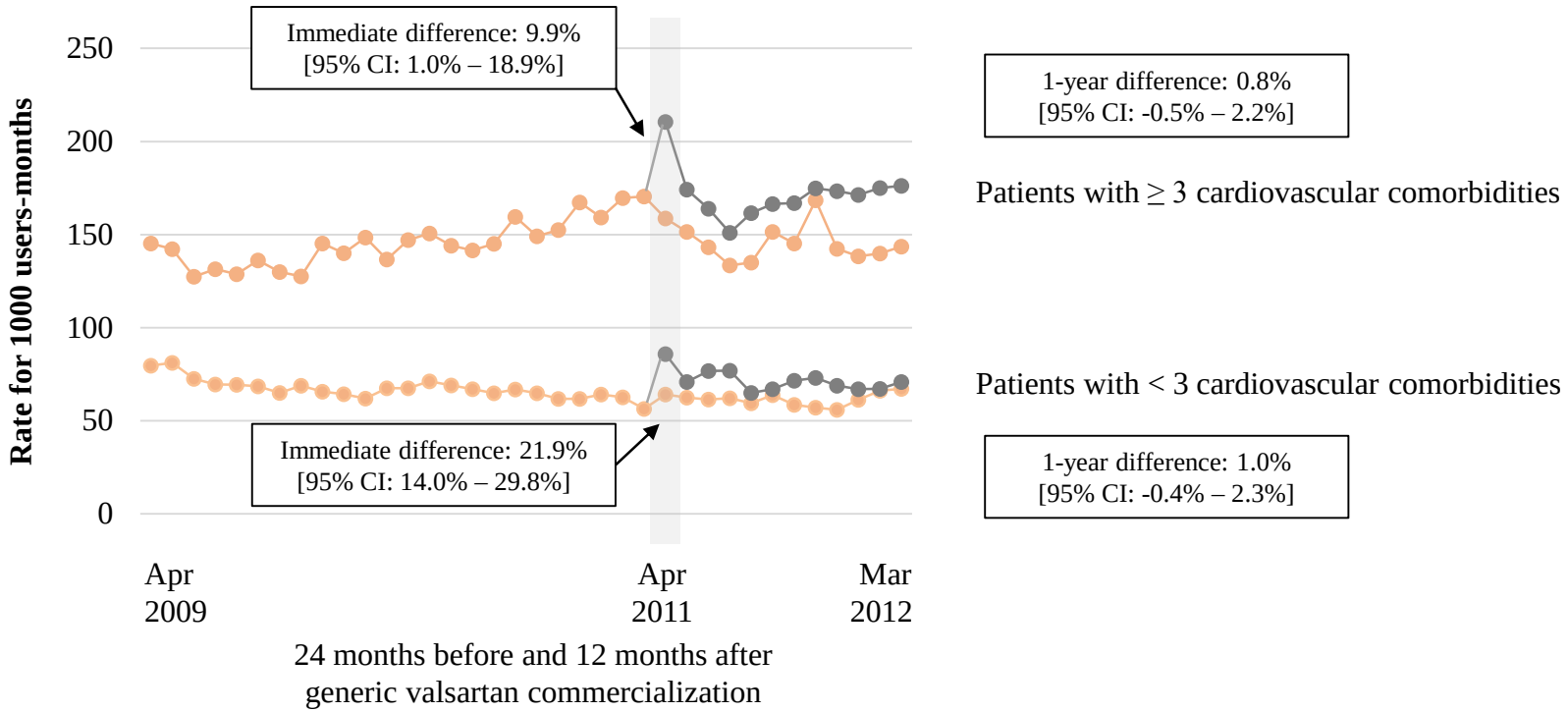


Figure S6c. Interrupted time series analysis of adverse events 24 months before and 12 months after commercialization of 3 generic candesartan analogs stratified for risk of adverse events

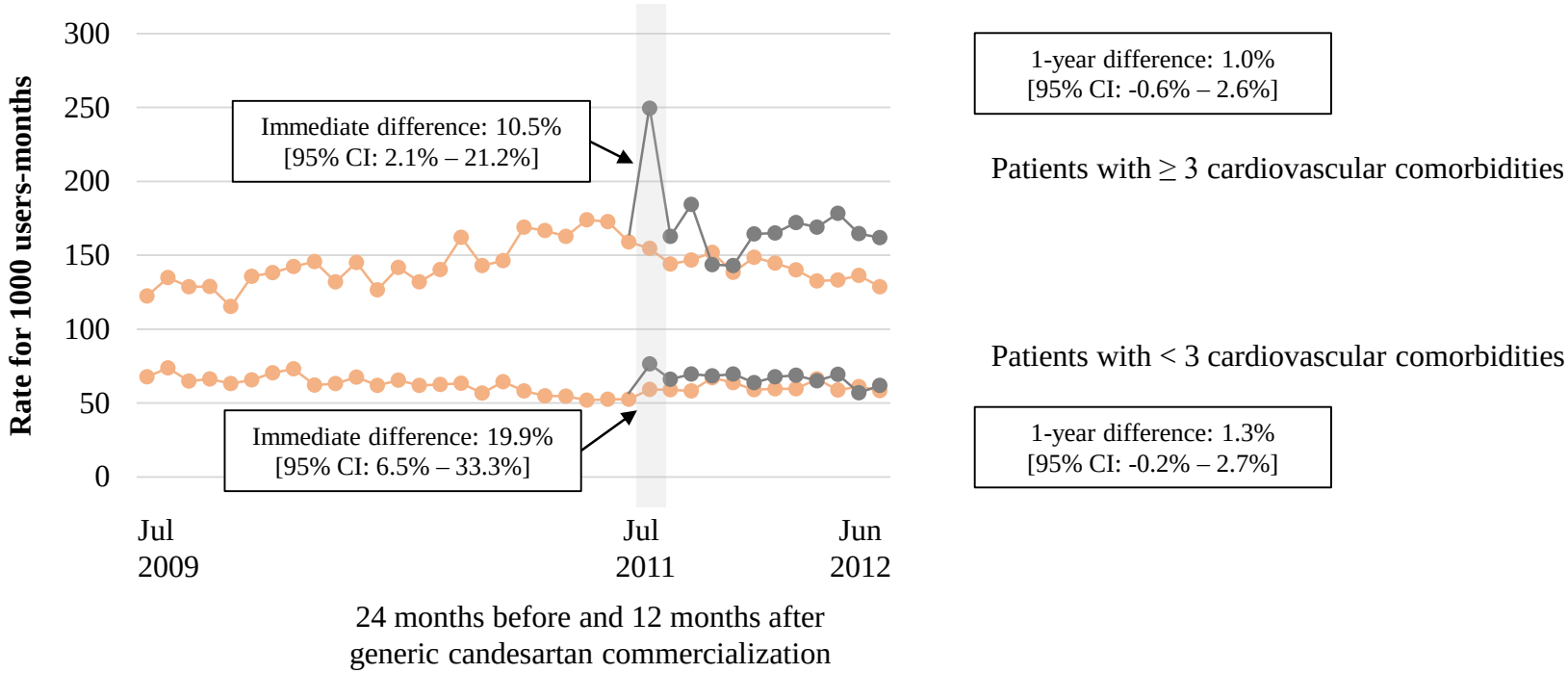


Figure Legend for Figures S6a, S6b and S6c

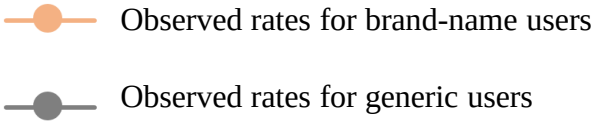


Figure S7a. Interrupted time series analysis of specific vs. non-specific cardiovascular adverse events 24 months before and 12 months after commercialization of 8 generic losartan analogs

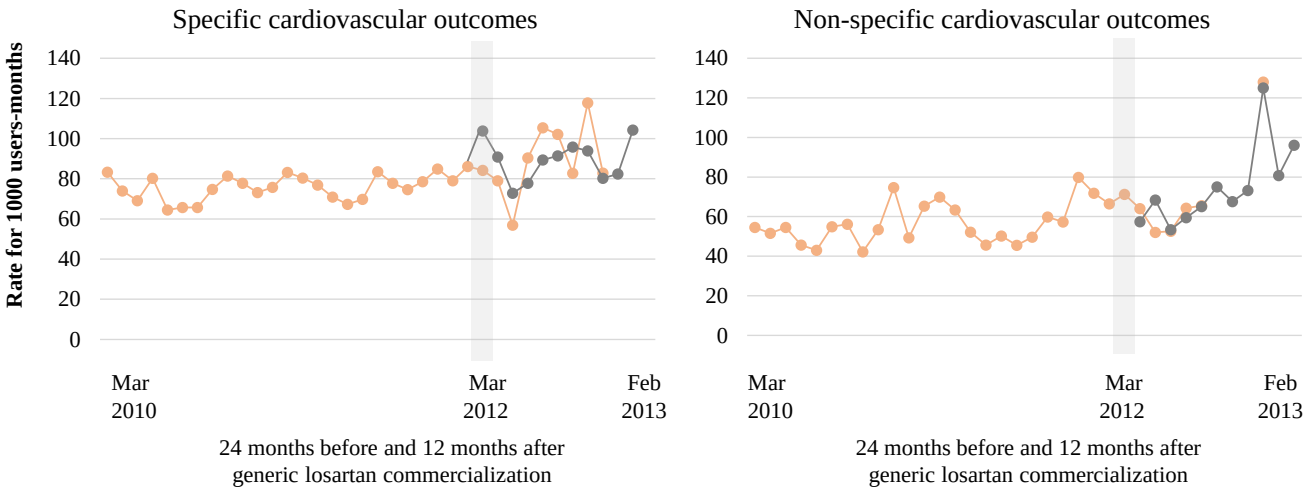


Figure S7b. Interrupted time series analysis of specific vs. non-specific cardiovascular adverse events 24 months before and 12 months after commercialization of 5 generic valsartan analogs

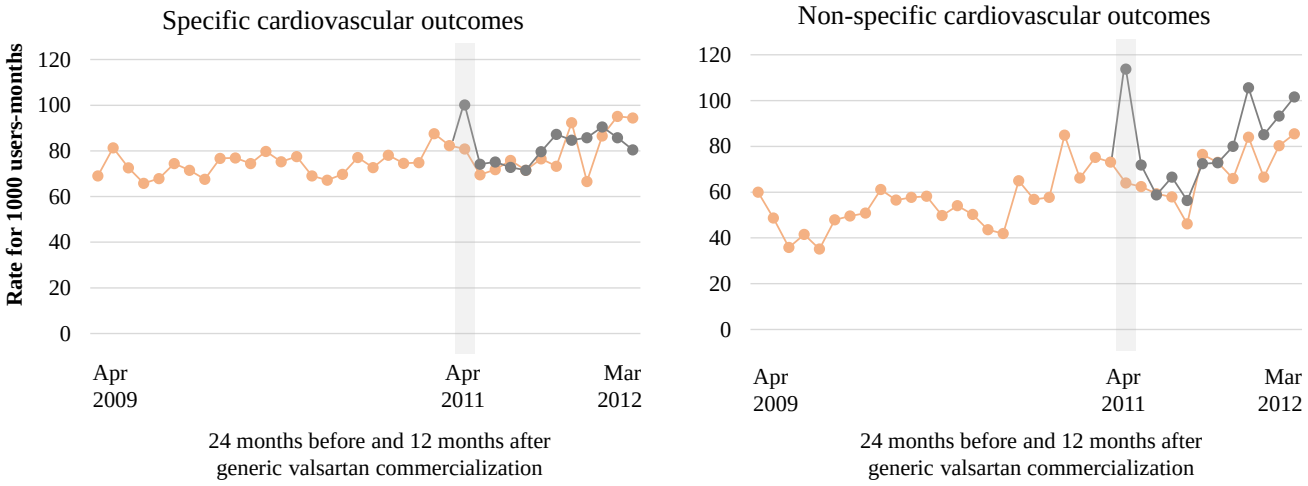


Figure S7c. Interrupted time series analysis of specific vs. non-specific cardiovascular adverse events 24 months before and 12 months after commercialization of 3 generic candesartan analogs

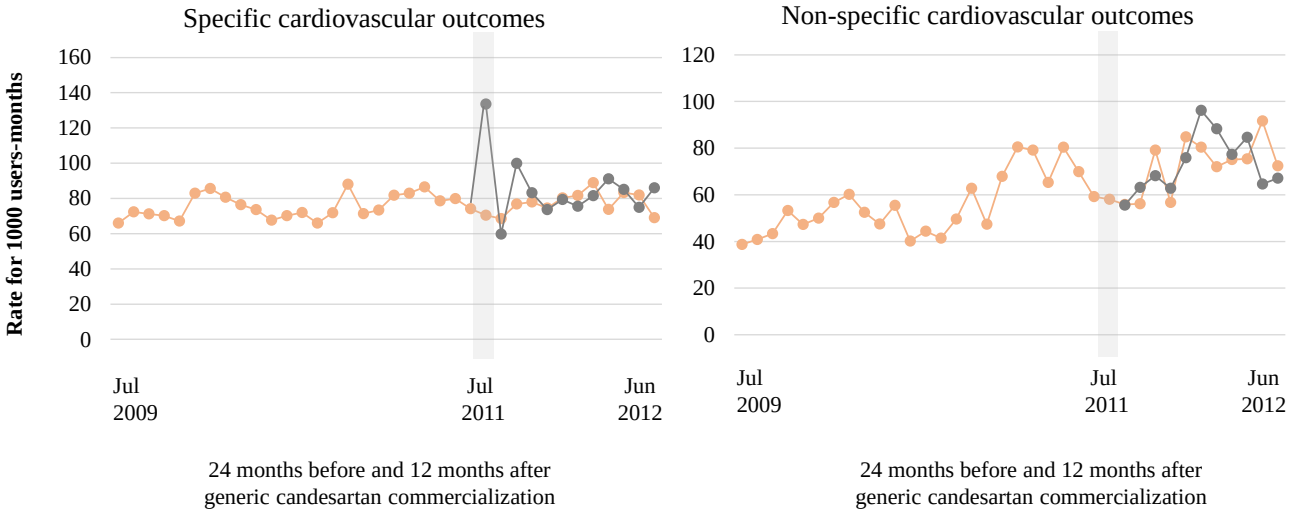


Figure legend for Figure S7a, S7b and S7c

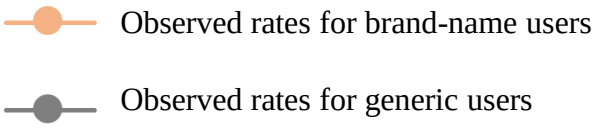


Table S5. Post-hoc descriptive characteristics of generic and brand-name losartan, valsartan and candesartan users during 1st and 2nd month after generics commercialization

Characteristics	**losartan**		**valsartan**		**candesartan**	
	Brand-name	Generic	Brand-name	Generic	Brand-name	Generic
Age (≥ 80 years old)	37.3	40.2*	35.4	37.5*	34.8	35.4
Women (%)	62.7	64.5*	60.0	58.5*	61.7	62.0
Comorbidities (number)						
All comorbidities	3.1 ± 1.9	3.3 ± 2.0‡	3.0 ± 1.9	3.2 ± 2.0‡	3.1 ± 1.9	3.2 ± 2.0‡
Cardiovascular comorbidities	2.2 ± 1.5	2.5 ± 1.6‡	2.3 ± 1.5	2.4 ± 1.6‡	2.4 ± 1.5	2.4 ± 1.6†
Concomitant drugs (number)						
Non-proprietary name	10.1 ± 5.8	10.8 ± 6.0‡	9.8 ± 5.9	9.9 ± 6.0†	9.9 ± 5.8	10.2 ± 6.0†
Socioeconomic status (%, lowest quintile is favoured)						
Social deprivation (lowest)	16.1	15.2	15.4	16.0	15.4	15.0
Social deprivation (highest)	22.2	24.8	23.1	23.3	22.8	24.7
Material deprivation (lowest)	22.3	16.5‡	18.1	12.9‡	18.4	14.5*
Material deprivation (highest)	19.3	23.2‡	21.4	25.7‡	20.1	23.4*
Region of residence (%)						
Urban (>1.5 million inhabitants)	54.7	45.8‡	49.3	34.1‡	49.7	33.0‡
Rural (< 10 000 inhabitants)	17.9	22.3†	19.6	27.7‡	19.0	24.8‡

Data are presented as proportions or mean ± standard deviations; statistical significance evaluated using the chi-square test or independent sample t-test; * means $p < 0.05$; † means $p < 0.01$; ‡ means $p < 0.0001$.

Table S6. Time series regressions parameters

Parameters	Estimate	Standard error	95% CI lower limit	95% CI upper limit	Chi square value	P value
Losartan: all users grouped together						
β_0: Intercept	-2.3050	0.0164	-2.3372	-2.2729	19771.99	<0.0001
β_1: Time (Before)	-0.0032	0.0011	-0.0055	-0.0010	8.07	0.0045
β_2: Commercialization	0.0280	0.0267	-0.0244	0.0804	1.09	0.2955
β_3: Time*Commercialization (After)	0.0065	0.0034	-0.0003	0.0132	3.52	0.0606
Dispersion	0.0009	0.0004	0.0004	0.0020		
Losartan: with a specific variable identifying generic and brand-name users						
β_0: Intercept	-2.3050	0.0169	-2.3381	-2.2720	18672.5	<.0001
β_1: Time (Before)	-0.0032	0.0012	-0.0056	-0.0009	7.61	0.0058
β_3: Commercialization	0.0046	0.0320	-0.0581	0.0673	0.02	0.8856
β_4: Generic*Commercialization	0.0768	0.0326	0.0129	0.1407	5.55	0.0185
β_6:Time*Commercialization (After)	-0.0172	0.0058	-0.0285	-0.0059	8.92	0.0028
β_7:Time*Commercialization*Generic (After)	0.0171	0.0070	0.0033	0.0309	5.92	0.0150
Dispersion	0.0010	0.0004	0.0005	0.0021		
Valsartan: all users grouped together						
β_0: Intercept	-2.3206	0.0153	-2.3506	-2.2906	22976.79	<0.0001
β_1: Time (Before)	0.0016	0.0011	-0.0005	0.0037	2.28	0.1306
β_2: Commercialization	-0.0161	0.0249	-0.0650	0.0328	0.42	0.5190
β_3: Time*Commercialization (After)	-0.0003	0.0032	-0.0066	0.0059	0.01	0.9149
Dispersion	0.0010	0.0003	0.0006	0.0019		
Valsartan: with a specific variable identifying generic and brand-name users						
β_0: Intercept	-2.3206	0.0161	-2.3521	-2.2891	20868.5	<.0001
β_1: Time (Before)	0.0016	0.0011	-0.0006	0.0038	2.07	0.1502
β_3: Commercialization	-0.0553	0.0270	-0.1082	-0.0024	4.19	0.0407
β_4: Generic*Commercialization	0.1107	0.0313	0.0493	0.1720	12.48	0.0004
β_6:Time*Commercialization (After)	-0.0066	0.0036	-0.0137	0.0005	3.30	0.0692
β_7:Time*Commercialization*Generic (After)	0.0012	0.0053	-0.0092	0.0117	0.05	0.8171
Dispersion	0.0012	0.0003	0.0007	0.0020		
Candesartan: all users grouped together						
β_0: Intercept	-2.3326	0.0163	-2.3646	-2.3007	20511.40	<0.0001

β_1: Time (Before)	0.0025	0.0011	0.0003	0.0048	4.80	0.0284
β_2: Commercialization	-0.0084	0.0265	-0.0604	0.0436	0.10	0.7518
β_3: Time*Commercialization (After)	-0.0084	0.0034	-0.0151	-0.0017	6.06	0.0138
Dispersion	0.0011	0.0004	0.0006	0.0021		
Candesartan: with a specific variable identifying generic and brand-name users						
β_0: Intercept	-2.3050	0.0169	-2.3381	-2.2720	18672.5	<.0001
β_1: Time (Before)	0.0025	0.0012	0.0001	0.0049	4.16	0.0413
β_3: Commercialization	-0.0264	0.0291	-0.0834	0.0306	0.82	0.3637
β_4: Generic*Commercialization	0.1310	0.0371	0.0583	0.2037	12.47	0.0004
β_6:Time*Commercialization (After)	-0.0141	0.0038	-0.0216	-0.0065	13.35	0.0003
β_7:Time*Commercialization*Generic (After)	0.0033	0.0060	-0.0086	0.0151	0.29	0.5893
Dispersion	0.0013	0.0004	0.0007	0.0024		

CI: confidence interval of the estimate. Before: 24 months before generics commercialization; Commercialization: Month of generics commercialization; After: 12 months after generics commercialization for generics users; Dispersion is a variable used with negative binomial regression models to control for overdispersion of variance.

Basic regression equation for all users grouped together

$$E[Y_i] = \exp\{\beta_0 + \beta_1 Time_i(\text{before}) + \beta_2 COM._i + \beta_3 (Time*COM.)_i(\text{after}) + \text{Dispersion}\}$$

Basic regression equation with a specific variable identifying generic and brand-name users

$$E[Y_i] = \exp\left\{\begin{array}{c}\beta_0 + \beta_1 Time_i(\text{before}) + \beta_2 Generic_i + \beta_3 COM._i + \beta_4 (COM.*Generic)_i(\text{after}) \\ + \beta_5 (Time * Generic)_i(\text{before}) + \beta_6 (Time*COM.)_i(\text{after}) \\ + \beta_7 (Time*COM.* Generic)_i(\text{after}) + \text{Dispersion}\end{array}\right\}$$

This equation implies that the reference group is made up of brand-name users before generic commercialization. Thus, it is easy to prove that the terms $\beta_2 Generic_i$ and $\beta_5 (Time * Generic)_i(\text{before})$ will always be zero since there is no rate for the group of generics before commercialization.

$$E[Y_i] = \exp\left\{\begin{array}{c}\beta_0 + \beta_1 Time_i(\text{before}) + \beta_3 COM._i + \beta_4 (COM.*Generic)_i(\text{after}) \\ + \beta_6 (Time*COM.)_i(\text{after}) \\ + \beta_7 (Time*COM.* Generic)_i(\text{after}) + \text{Dispersion}\end{array}\right\}$$

References

1. Pampalon R, Hamel D and Gamache P. A comparison of individual and area-based socio-economic data for monitoring social inequalities in health. *Health Rep*. 2009;20:85-94.

2. Vittinghoff E. Regression methods in biostatistics: linear, logistic, survival, and repeated measures models New York: Springer; 2012: 340.

3. Hellstrom J and Rudholm N. Side effects of generic competition? *Eur J Health Econ*. 2004;5:203-8.